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## ORIGINAL ARTICLES.

### UNUSUAL SYMPTOMATOLOGY WITH TUMORS OF THE CEREBELLUM BASED ON 158 VERIFIED CASES.

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The diagnosis of the presence of a tumor of the cerebellum presents few difficulties in the typical case. However, in the absence of characteristic neurologic signs, localization may be uncertain. The obscure case of cerebellar tumor may be attended by unexpected complications for which the surgeon may be totally unprepared. This report proposes to call attention to unusual cerebellar symptomatology and findings which are emphasized in order to clarify diagnosis of the atypical case. The unusual rather than the usual findings have determined the pattern of this report.

The point may be raised that final decision in a questionable diagnosis of tumor of the cerebellum rests upon results of ventriculographic study. This is unquestionably true in most instances. However, it is equally true that the interpretation of the ventriculogram is aided by an appreciation of all clinical possibilities. Also, doubtful pneumographic findings occur, and frequently in the clinically puzzling cases.

The material presented includes the diagnostic findings present in 158 cases of verified tumor of the cerebellum. The review is summarized graphically where possible. A number of findings required a more detailed analysis. These will be considered and, when pertinent, illustrated by case reports.

**Summary of Findings.** *Convulsions.* Motor convulsions were present in 21 and attacks of loss of consciousness occurred in 13 cases,

making a total of 34 instances of the convulsive state (21.5%). In 11 instances the lesions, in this group of patients, was in the midline; in 22, in the right or left lobe of the cerebellum. In 1 case the tumor was reported as invading both cerebellar lobes. Papilledema was present in greater or in less degree in 31 cases. One patient had no papilledema; in 2 there was no record of the fundus examination. The manifestations of the convulsive state were as follows:

TYPE OF CONVULSIONS

| Type | Instances | Autopsies |
|---|---|---|
| Segmental—clonic | 7 | 3 |
| Generalized: | | |
| Clonic | 3 | 3 |
| Tonic | 11 | 4 |
| Syncopal | 13 | 3 |

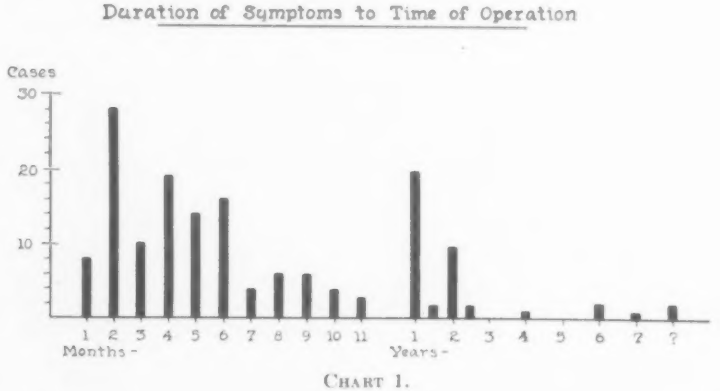


CHART 1.

Syncopal attacks which occurred commonly in an early or middle period of the patient's disease may be illustrated by the following instance:

CASE 1.—A 25-year-old woman, complained of pain in the right ear, headache, unsteadiness of gait and numbness of the right side of the face in

April, 1925. Symptoms were first noticed in October, 1923, when she experienced pain in the back of the head and in the neck. In February, 1925, the patient noticed difficulty in walking and impairment of vision in the right eye. In March, unsteadiness of gait increased. She had twitching of the muscles of the right side of the face and lips. During this month also she had fainting attacks which occurred 4 to 5 times daily. During the attacks which lasted about 1 minute, she was unconscious and became cyanotic. Recovery was rapid as profuse perspiration occurred. Neurologic examination showed the patient to be hypotonic. Three diopters of papilledema were present in the right eye and 2 in the left. Incoördination could not be demonstrated in the extremities although the patient tended to fall to the right in gait testing. Horizontal nystagmus was present on lateral gaze; there was a weakness of the right side of the face. At operation, a cyst of the right lobe of the cerebellum was evacuated.

An example of the clonic-segmental type of convulsion is shown by the following case which is described in brief:

CASE 2.—A 38-year-old male carpenter, was well until December, 1930, when he began to vomit. In April, 1931, headache followed upon attacks of vertigo. At this time, also, the patient began to have spells of shaking in both upper extremities. The tremors were rapid and coarse occurring every

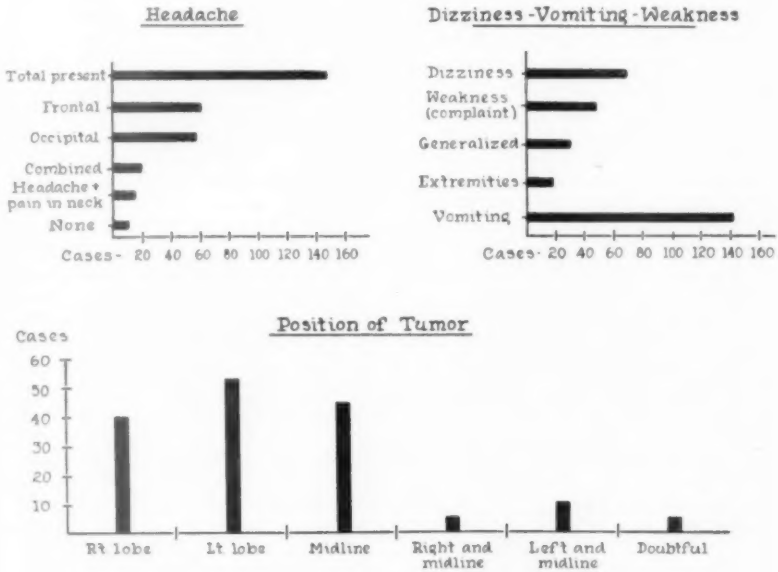


CHART 2.

2 days. Examination the following month showed a mentally dull patient who held his head in pain. There was a moderate hypotonia of the left upper extremity; finger-to-nose testing showed a slight ataxia and dysmetria of the right upper extremity; rapidly alternating movements were impaired in both hands. The patient was unable to raise himself from the dorsal decubitus position without the use of the arms. Reflexes were pendulous in the lower extremities. There were 2 diopters of papilledema present.

Nystagmus was absent. While being examined, the patient had "mild, fairly rapid, pseudo-clonic jerkings of the shoulder girdle muscles, the muscles of the arm and forearm lasting for 30 seconds. There was no typical distribution of the clonic contractions. They were not the usual flexor type seen in cortical irritation and they caused no regular pattern of movement of the extremities. Palpitation of the muscles during the convulsions indicated that the contractions were more of the nature of a clonic affair than a tremor." Routine Roentgen studies were normal. A ventriculogram was recommended to localize the lesion. The patient was given a colonic irrigation because of constipation and because an enema was considered unwise in view of the unknown localization of the tumor. After an hour of irrigation, the patient was described as the picture of shock. At this time Dr. Charles H. Frazier saw him have "a definite clonic convulsion of his upper extremities." Death occurred 12 hours after a ventricular trephine. Autopsy showed a pronounced hydrocephalus with a pressure cone and a right cerebellar cyst.

*Visual Field Defects.* Significant and confusing alterations in the visual fields were found to be present in 8 cases. Reliance placed upon the perimetric examination as a diagnostic aid served to make the occurrence of such defects a false localizing sign of major importance. The defects were classified as follows, some of which are demonstrated in Figure 1: Homonymous hemianoptic defects, 4; bitemporal hemianoptic defects, 1; unclassifiable, 3.

Case 3 demonstrates how such a finding may confuse the diagnosis.

Case 3.—The patient was a 54-year-old male. A year before admission, he noticed a dull ache in the back of his neck. This became increasingly severe. Four months before admission, his gait became unsteady. Irritability and failing memory with drowsiness then became outstanding complaints. The neurologic examination was inconclusive insofar as furnishing localizing information. There were marked mental disturbances and questionable aphasic manifestations. Roentgen examination of the skull showed the pineal body calcified and in the midline. The optic disks were normal except for the presence of a small flame-shaped hemorrhage in the right retina. The visual acuity seemed normal to the examiner although no visual notations were made. Perimetric examination revealed the presence of a right homonymous hemianopsia. Although the available findings suggested a lesion either in the occipital or temporal lobe, the lack of evidence of increased intracranial pressure made pneumographic studies necessary for precise diagnosis. Ventriculography showed a marked symmetrical dilatation of the ventricular system. In view of this, a suboccipital craniectomy was performed. A cystic hemangioma was found in the left cerebellar lobe.

*Other Ophthalmologic Findings.* Papilledema was present in 126 instances and absent in 15. In the remaining 17, the finding was not recorded or was equivocal. Of the 15 cases in which papilledema was absent, 3 were 13 years old and the remainder were in the age group of 20 to 41. The survey Roentgen examination in this group was negative in 9 cases. In 7, ventriculograms were made and all showed hydrocephalus. In 2, unsatisfactory encephalograms were done. The onset of symptoms in the group showing no papilledema dated from 2 weeks to 1 year before admission. In 2 cases the

patients died unexpectedly, 1 in spite of emergency surgery. Although papilledema was absent, hydrocephalus was found either by ventriculography or autopsy in 9 cases.

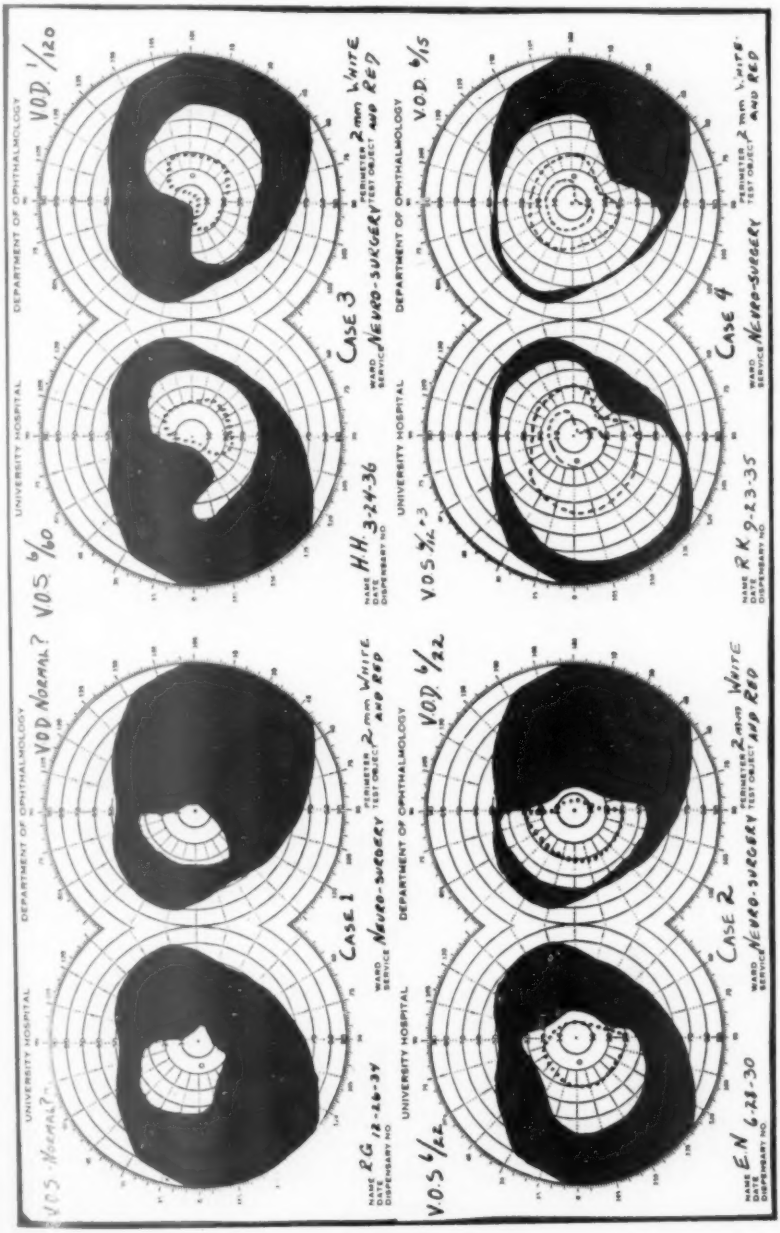


FIG. 1.—Representative visual field charts of a group of 8 patients showing confusing defects.

The complaint of impaired or failing vision was common, being present in 50% of the cases. In 6 instances, this complaint was present in the absence of papilledema. Eleven patients were blind in both eyes; 3 had unilateral loss of vision on admission. Three of

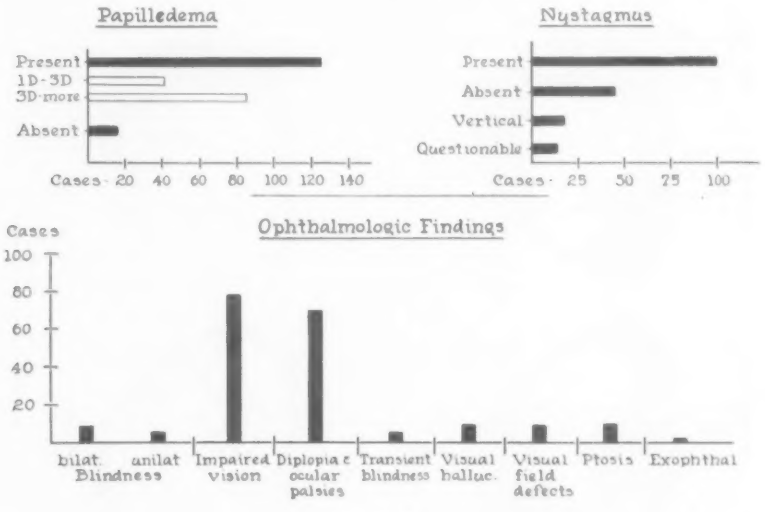


CHART 3.

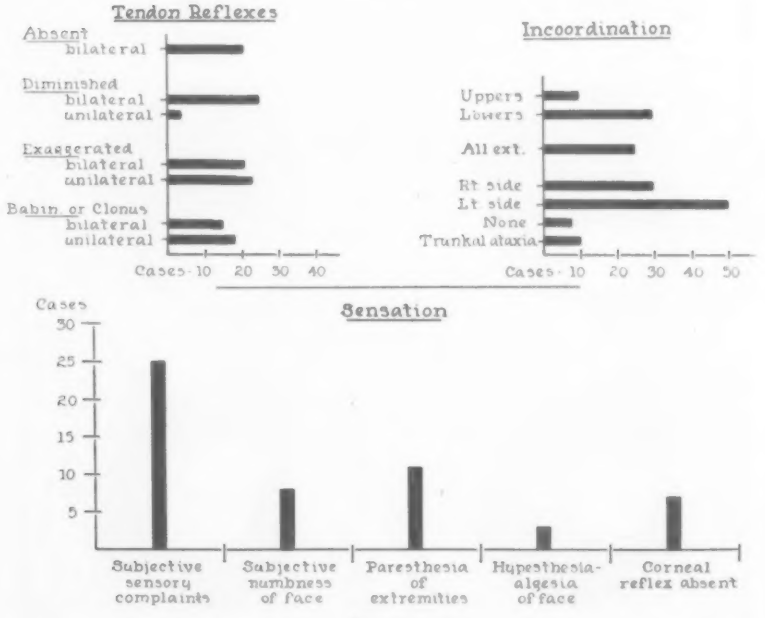


CHART 4.

the 11 patients who were completely blind at the time of admission had rapid loss of vision through a period ranging from 8 weeks to 3 months which was associated with marked papilledema. Two patients had sudden, complete loss of vision. None of the group, who was blind on admission, recovered sight.

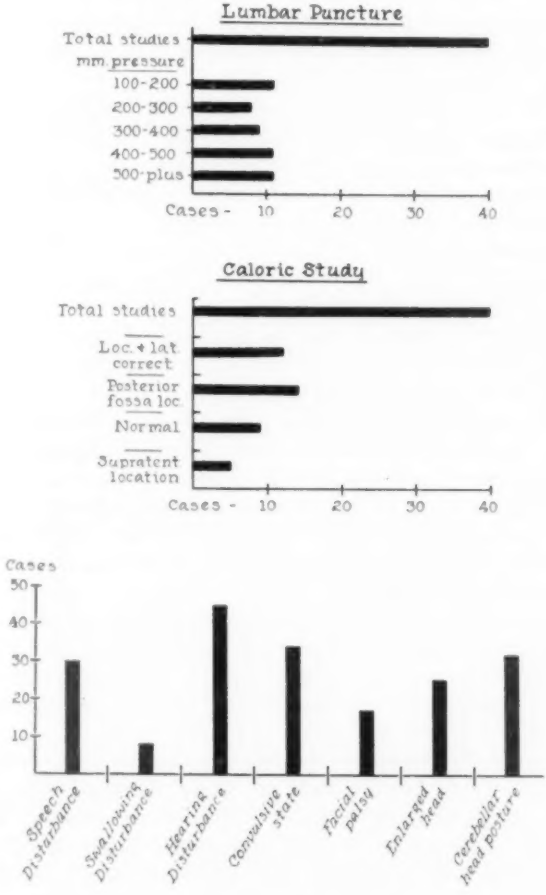


CHART 5.

Transient attacks of blindness occurred in 5 patients. This was always a late symptom. One of these patients described frequent attacks of blindness. About once an hour she became "stone blind for 2 or 3 minutes." Between attacks she thought her vision normal. (Measurement of acuity was 6/9 02.) Papilledema of 5 diopters was present.

Visual hallucinations were complained of by 8 patients. The hallucinations were described as follows:

1. Saw different colors before eyes.
2. Saw wild cherries, grapes, haystacks and fires burning.
3. Saw streaks before eyes which were dark during the day and light at night; at night frequently saw balls of light before the eyes.
4. Hallucinations wherein the patient stopped his truck thinking that he had seen a bad accident.
5. Had hallucinations of formed images of men and autos.
6. Saw scotomata and shadows.
7. Saw scotomata early; this was followed by subjective images of dogs, cats, mice, bugs, spiders, light flashes.
8. Saw light flashes and subjective images.

All these 8 patients noted concomitant impairment of vision. Advanced papilledema was present in each.

It is noteworthy that 11 patients had third nerve palsies, in 2 instances bilaterally. In 1 case this finding led to an incorrect supratentorial exploration.

The majority of cases showed nystagmus. In 41 instances, however, this sign was absent. Moreover, incoördination was absent in 8 members of this group and reported as minimal in 4. All except 2 of the 41 cases showed evidence of increased intracranial pressure either by Roentgen study or by the presence of papilledema. A right or left lobe tumor was present in 29; a midline tumor in 12.

Vertical nystagmus was observed in only 18 patients. In 17 cases of the 18 horizontal nystagmus was also present. A midline tumor was found in 12 of these patients while in 6 the lesion was located in either cerebellar hemisphere.

*Lumbar Puncture.* Lumbar puncture was performed in 50 cases. It is noteworthy that in 11 the spinal fluid pressure was within normal limits (100 mm. to 200 mm. of water). In these 11 cases papilledema was absent in 4. The remaining 7 showed variable degrees of papilledema.

*Roentgenographic Studies.* In 108 cases a survey roentgenologic study was made. Two-thirds of these studies were reported negative. Approximately one-third of the cases showed Roentgen evidence of increased intracranial pressure. Other qualified diagnoses in addition to increased intracranial pressure signs were as follows:

| | |
|---|---|
| Calcification in the tumor mass | 2 |
| Rarefaction in bone overlying the lesion | 3 |
| Petrous ridge erosion | 3 |
| Parasellar lesion in right middle fossa | 1 |

Ventriculography was performed in 37 cases. In a number of instances, ventricular estimations were carried out. The finding of bilaterally enlarged ventricles, in the latter procedure, precluded the necessity of air injection. An internal hydrocephalus was ob-

served in 21 of the 37 studies. In 2 cases, the diagnosis of "top normal" ventricles was made. A supratentorial localization was incorrectly made in 5 cases. Two other patients were diagnosed as having third ventricular tumors. Lateral ventricular defects were noted in 5 cases; in 2 of these a defect was present in the body of one ventricle; in 2, a unilateral posterior horn deformity was diagnosed and in one there was asymmetry of the lateral ventricles. Three cases showed defects in the fourth ventricle, one accompanied by hydrocephalus.

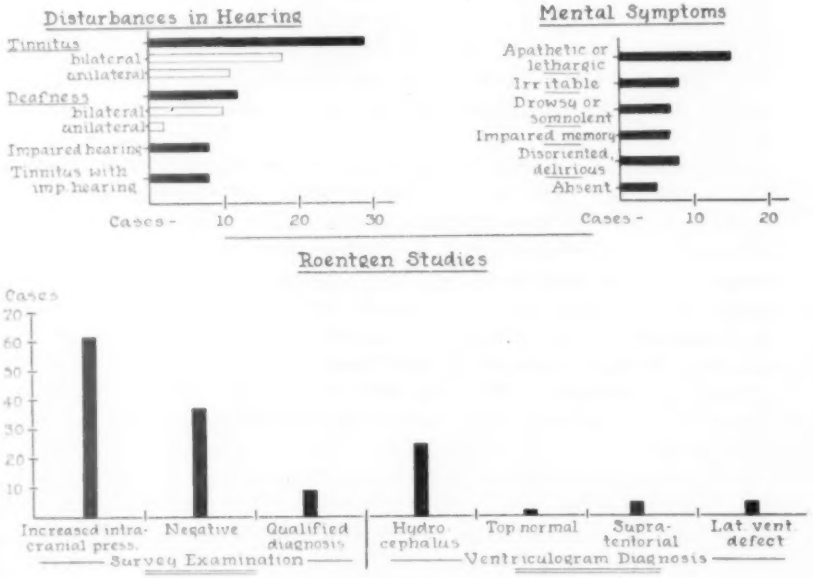


CHART 6.

*Sensory Phenomena.* Sensory complaints and signs were not rare. Numbness of the face was complained of by 8 patients. Paresthesias including the tongue, arm, hands, trunk, fingers and lower extremities were noted in 11 cases. Anesthesia of one cornea was present in 7 instances. Questionable findings upon the latter point were excluded. Objective impairment of sensation in the remaining distribution of the fifth nerve was observed in 3 of the 7 patients. Four members of this group also had facial palsies.

*Caloric Examination.* In 14 cases the caloric examination failed to indicate the presence of posterior fossa tumors which were subsequently found. In 5 instances the examination was misleading, suggesting a supratentorial lesion. Review of these cases failed to suggest any correlation of findings to account for the results of the examination.

*Tendon Reflexes.* The tendon reflexes did not appear to conform to a uniform pattern. In the majority of cases, the tendon reflexes were normal. Exaggerated reflexes, either unilateral or bilateral, were encountered in 44 cases, while in 33 clonus or an extensor plantar reflex was elicited.

*Cranial Nerve Palsies.* A facial palsy was definitely reported in 17 cases. In 19 a slight facial palsy was recorded, and in 6 others this sign was indicated as being questionable. Symptoms referable to the eighth nerve were present in 57 patients. Deafness or impaired hearing was present in 28 cases and tinnitus was complained of by 29. Four cases presented the syndrome of the cerebello-pontine angle, having palsies of the 7th, 8th and 5th nerves. In each instance, no compression of the nerves could be visualized at operation. In addition, 6 cases showed involvement of the 7th and 8th nerves and 3 of the 7th and 5th.

**Discussion.** The diagnosis of tumor of the cerebellum is both aided and complicated by the development of a rapid and early hydrocephalus which results from the strategic position of the tumor. Although increased intracranial pressure is characteristic of the cerebellar syndrome, false localizing signs may arise from the secondary hydrocephalus produced. As a result, early focal signs may be lost or overshadowed by prominent secondary effects. Collier[4] drew attention to the occurrence of false localizing signs due to increased intracranial pressure. He concluded that in the presence of advanced tumor of the brain with hydrocephalus, focal signs lost importance.

It has been suggested that false localizing signs due to increased intracranial pressure and hydrocephalus are cerebellar in character. Nystagmus, hypotonia, tremor, staggering and deviation in walking are frequently noted. Examples of such instances have been reported by Young,[34] Bramwell,[3] Oppenheim,[17a] Spiller,[24] Rhein[20] and others. Wakeley and Allen[27] stated that cerebellar signs which are not absolutely definite and develop with or after the appearance of general symptoms of increased intracranial pressure are false localizing signs and as such are of no value whatever in determining the site of the lesion.

In our experience there are other false localizing signs which occurred in the presence of tumors of the cerebellum with secondary hydrocephalus which deserve emphasis. The rôle that increased intracranial pressure plays in the production of these signs, we believe, is dominant. Evidence on this point is shown in the occurrence of convulsions and visual field defects which are discussed in detail.

*Convulsions.* The tonic "cerebellar fit" has been recognized as the characteristic convulsive pattern frequently present in patients with tumor of the cerebellum. Description of this type of convulsion was made by Wurffbain[33] in 1691 and later defined by Jackson.[14a]

Attention has been given mainly to the tonic convulsion although it has been recognized that other patterns occur. This fact is mentioned by Jackson himself who quoted case reports of clonic convulsive movements in patients with tumor of the cerebellum and by Oppenheim,[17b] Stewart,[25] Collier[4] and others. Collier in particular emphasized the occurrence of clonic as well as tonic convulsions as a false localizing sign in cases of tumor of the cerebellum when increased intracranial pressure was established.

A consideration of the findings here reported showed that a variety of types of convulsions occurred. These ranged from syncopal attacks located at one end of the "convulsive spectrum" to tonic fits at the other. Attention in the literature has been given mainly to the tonic cerebellar fit and a number of explanations have been offered to account for it. It is logical, however, that if other varieties of convulsive seizures occur, they too demand an explanation. Furthermore, it is reasonable to suspect that a common mechanism accounts for the various convulsive manifestations.

A review of the literature on this subject was recently made and reported.[28] A conclusion arrived at was that both the tonic cerebellar fit and the other types of convulsive phenomena were expressions of temporary cerebral anemia. This explanation was based upon the experimental work of Cushing,[5c] Eyster, Burrows and Essick,[9] and Wolff and Forbes,[32] all of whom showed that sudden increases of intracranial pressure produced convulsions. The convulsions were the result of the temporary cerebral anemia caused by elevating the intracranial pressure above the systolic blood pressure. The same chain of events may follow when a patient with increased intracranial pressure suddenly increases the pressure by straining at stool, vomiting, struggling, and so on. The tonic cerebellar fit was therefore described as a *decortication phenomenon* not as a *decerebration phenomenon* for it does not seem likely that cerebellar tumors can cause a physiologic transection of the brain stem. Tonic fits may be seen in a variety of pathologic conditions which have in common physiologic or pathologic decortication.

It was also pointed out that ischemia of the brain may manifest itself initially by exaltation of function accounting for the occasional presence of convulsions of the cortical excitatory type. On the other hand, syncope may be the first and the mildest expression of transient cortical ischemia.

In brief, there is sufficient physiologic information at hand to account for the occurrence of various types of convulsions with tumors of the cerebellum on the basis of alterations in cerebral bloodflow. These alterations in bloodflow can be occasioned by transient changes in the relationship of the intracranial pressure to the systolic blood pressure.

*Visual Field Defects.* For the purposes of focal neurologic diagnosis, it is generally accepted that visual field defects indicate direct

involvement of the visual pathways at some point. This is thought to be so reliable that often intracranial operations are planned and performed solely on the information obtained from examination of the visual fields.

In the material reviewed, visual field defects resulting from the effects of distant lesions upon the visual pathways were noted in 8 cases. In most instances they appeared so significant to the examiners that the diagnoses were confused and it became necessary to rely upon pneumographic studies to establish the correct site of the tumors.

Although visual defects are an unusual finding in cases of tumor of the cerebellum, a number of cases have been reported. Gowers[11] was aware of their occurrence; Oppenheim[17c] mentioned that he had seen the middle portion of the optic chiasm so compressed by a bulging third ventricle that in 1 case "only two thin threadlike processes showed the course of the optic nerves." The latter stated that cerebellar tumors may produce ventricular distention and so be the cause of a bitemporal hemianopsia. Wohlwill[31] also stated that in hydrocephalus, the protruding third ventricle may compress the chiasm against the sella and produce bitemporal hemianopsia or simple optic atrophy. Cushing cited a case of distended third ventricle resulting from a blocked cerebral aqueduct which produced a combination of optic atrophy and bitemporal hemianopsia. Cushing and Walker,[7] in an early paper, discussed the occurrence of binasal hemianopsia associated with cerebellar tumors.

Theoretically at least, since internal hydrocephalus and a distended third ventricle eventually accompany all cases of cerebellar tumors, evidences of chiasmal compression should not be unusual. This is apparently not the case. In many instances the hydrocephalus is minimal and the patient is operated upon before late symptoms occur. The anatomic relationship between the third ventricle and the chiasm is a second factor. As Schaeffer[23] showed in his fundamental anatomic researches on the optic chiasm, this structure is not always in the same position. In only 12% of the bodies examined was the relationship exactly as depicted in standard anatomies. Thus, variations in the position of the chiasm allow many different anatomic relationships with the downwardly distending third ventricle.

De Schweinitz,[8] in the Bowman Lecture, devoted a section to anomalies of the arteries comprising the Circle of Willis. He described how indentations of the optic nerves and chiasm could be produced by these vessels if, as frequently occurs, the chiasm were dislocated. He showed how the posterior communicating artery, as it runs beneath the optic tract, could produce an homonymous hemianopsia if the distended third ventricle pushed the optic nerve against the vessel.

In the group of patients with visual field defects here reported, a

marked distention of the third ventricle was found in every case in which ventricular studies were performed or where necropsy was permitted. It is reasonable to believe that the distended third ventricle may have produced the defects found. As a corollary point, the presence of a visual field defect in a case with increased intracranial pressure does not exclude the presence of a tumor of the cerebellum.

*Other Ophthalmologic Findings.* Papilledema was reported as absent in 15 cases in which a tumor of the cerebellum was later found. It is recognized that this absence is not unusual in the presence of widened cranial sutures. Twelve of the cases, however, were beyond 20 years of age. In a number of instances, absence of this finding confused the diagnosis.

Jackson[14b] in 1881 reported upon the absence of choked disk in 3 patients, 2 of whom had lesions of the cerebellum. van Wagenen[26] reviewed 1 year's series of cases from Cushing's clinic and found that of 45 subtentorial tumor cases, 6 showed no papilledema. Three of these were cases of cerebello-pontine angle tumors. Cushing and Bordley,[6] in a clinical and experimental investigation of the subject, stated that they believed that the tendency of disks to develop papilledema varied greatly, thus accounting for variations in the presence of increased intracranial pressure. The literature indicates that the finding of papilledema in patients with a tumor in the posterior fossa is apparently higher than in cases with supratentorial lesions. Paton[18] and Brain[1] found normal fundi in approximately 20% of cases with supratentorial tumors. Others have reported an even higher percentage. The strategic position of the posterior fossa tumors would seem to account for the difference. The fact remains, however, that papilledema may be absent in the patient with a tumor of the posterior fossa although elevation of the intracranial pressure exists.

The incidence of failing visual acuity was high in patients with tumors of the cerebellum. Eleven cases were totally blind at the time of admission to the hospital while 3 were blind in one eye. Cushing[5b] reported a similar high incidence of visual loss. Of 61 cases of medullo-blastomata, 26 were reported to have impaired sight at the time of admission and 9 were blind. Cushing[5a] pointed out that the "symptomatic onset (of a case of tumor of the cerebellum) may relate to vision alone." This observation has been confirmed.

Transient attacks of blindness occurred in 5 patients and was of late occurrence in the course of the patient's disease lasting from a few minutes to several hours. De Schweinitz[8] stated that periods of temporary amaurosis may occur as part of the ocular symptomatology of hypophyseal tumor exactly as they do in ordinary brain neoplasms. "They depend upon pressure on the chiasma from the third ventricle." The fact that such attacks were observed to occur

only late appears to support De Schweinitz's observation. Cushing,[5a] however, reported a case in which the onset of the patient's illness was marked by periods of fleeting blindness. An alternate explanation may be transient disturbances in central bloodflow—the blindness expressing the disturbance in the occipital lobes.

The occurrence of visual hallucinations in cases of tumor of the cerebellum is an interesting finding. There were 8 such instances concerning which the information appeared to be reliable. The localizing importance of this finding has been emphasized in neuro-ophthalmologic literature, and modern textbooks of neurology suggest that it is possible to differentiate a lesion of the temporal pole from that of the occipital on the basis of the type of visual hallucination experienced. Brain and Strauss,[2] Wechsler,[29] Grinker[12] and Purves-Stewart[19] in their textbooks stated that visual experiences associated with lesions of the occipital lobe are confined to flashes of light and color and other so-called simple phenomena, while complex and elaborate images are found associated with lesions of the temporal lobe. According to these concepts, it would appear that visual hallucinations due to other lesions are unusual. Their occurrence in patients with tumors of the cerebellum, therefore constitute false localizing signs. Weinberger and Grant,[30] in a review of the subject of hallucinations associated with brain tumors, pointed out that the current conceptions of the localizing value of hallucinations may not be in keeping with the facts. The concept that certain areas of the cortex are so highly organized psychically as to produce visual hallucinations on stimulation by a tumor is neither sound physiologically nor psychologically. Visual hallucinations are highly integrated and complicated psychologic phenomena and require the activity of the entire brain. They may be excited, as these writers have shown, from any level of the neuro-optical apparatus. In their analysis of the published cases of hallucinations accompanying brain tumors, they pointed out that no localizing significance can be attached to the complexity of the images seen; that the hallucinations do not necessarily appear in the hemianoptic field and that tumors invading only the optic nerves may yield hallucinations indistinguishable from those reported in occipital or temporal lobe tumors. The hallucinations that occurred in patients with tumors of the cerebellum add further evidence to support that conclusion. It would be reasonable to suspect the dilatation of the third ventricle with compression of the optic chiasm as the cause of the phenomenon.

In the material reviewed, there were 41 cases in which nystagmus was absent and 18 which showed vertical nystagmus. Holmes[13] stated that very few lesions of the cerebellum fail to show nystagmus in some form or other. This finding, he reported, was absent in 3 cases of gunshot injuries that he studied but it occurred in all of his cases of cerebellar tumors. The presence of this finding, we

have noted, focuses attention to the cerebellum immediately; when absent, however, doubt as to posterior fossa localization was raised in a number of cases. Nystagmus is apparently considered to be an important criterion of cerebellar disease.

Cushing[5a] pointed out in a review of cases of astrocytoma of the cerebellum that "nystagmus is often wholly absent or represented by merely a few fine, poorly sustained twitches." Keschner and Grossman[15] reported horizontal nystagmus as present in 23 of 29 cases of intracerebellar tumors. In 9 instances, the nystagmus was also vertical in direction. These authors further stated that they did not find any correlation between the degree of intracranial pressure or the degree of asynergia and nystagmus. We were able to confirm this statement.

Vertical nystagmus was noted by Holmes[13] to "occur more commonly when the vermis was involved though it may be seen when the injury is limited to one half of the cerebellum." Of 18 instances of vertical nystagmus which were observed in our series, 12 patients had lesions involving the vermis. Fisher and Glaser[10] have emphasized the point that the presence of vertical nystagmus is pathognomonic of intrinsic brain disease since the phenomenon is never produced by a peripheral lesion.

*Lumbar Puncture.* It is interesting that lumbar punctures were performed without untoward results in 50 cases with tumors of the cerebellum. In 11, the pressure was normal. In 4 of the latter group, papilledema was absent, thus serving to confuse the diagnosis. A number of observers commenting on this finding felt that the absence of increased intracranial pressure, as indicated by the intraspinal pressure, ruled out the presence of a posterior fossa tumor. Although Cushing[5c] suggested that lumbar puncture was "hazardous as it may tend to a sudden wedging of the bulb," others have not found it so. Masson[16a] reported 32 cases of tumor in or around the cerebellum in which serious symptoms did not follow the withdrawal of a small amount of fluid by lumbar puncture. Earlier recognition of cases with tumor of the cerebellum may account for hospitalization before clinical evidence of increased intracranial pressure occurs. Thus a tumor of the cerebellum apparently cannot be ruled out on the basis of either a normal spinal fluid pressure or absent papilledema.

*Roentgenographic Studies.* Survey Roentgen examination aided in diagnosis by showing signs of increased intracranial pressure in one-third of the cases examined. Indirect localizing signs of tumor other than well-known evidences of increased intracranial pressure were wanting except in a few instances. Rossier[21] has reported a characteristic deformity of the basilar plate in 14 of 28 cases of cerebellar tumor, an interesting finding upon which our material does not permit comment. Masson[16b] reported an incidence of 12% of calcification in 25 cases of medullo-blastomata and 20% in

29 cases of astrocytomata. Although we have found a low incidence of calcification, this finding may be an aid to diagnosis as Roentgen technique and apparatus improve.

There was ventriculographic evidence of a posterior fossa tumor in 21 of 37 instances in which the procedure was performed, a procedure reserved for cases of obscure diagnosis. In 12 cases, the Roentgen evidence suggested supratentorial lesion. Ventricular estimation employed in place of ventriculography was a source of error in 3 of the total of 5 incorrect final diagnoses resulting in supratentorial explorations.

*Sensory Phenomena.* Subjective sensory complaints were not unusual and have been occasionally reported by others. Sargent and Greenfield,[22] in the case of a cyst of the cerebellum, reported that the patient had attacks of a tingling sensation in the left arm extending to the face. Similar types of sensory attacks were present in 11 members of our group of cases. Loss and diminution of corneal sensation were also observed. It would appear possible that sensory phenomena occur probably as a result of increased intracranial pressure as pointed out by Collier.[4]

*Caloric Examination.* Caloric examinations which were carried out in 41 patients of this series were misleading in 5, suggesting a lesion above the tentorium, and normal in 9. Various results have been reported as to the efficiency of this diagnostic procedure which appears to depend upon the astuteness of the examiner. Fisher and Glaser[10] reported excellent localizing results. Of 25 cases, only 3 were not localized to the side of the lesion and but 1 was wrongly placed. On the other hand, Keschner and Grossman[15] stated that in 29 cases, the "results of the tests were in full accord with the neurologic results in 6 cases." They believe that the caloric tests are considerably more valuable and reliable in localizing cerebellopontine angle tumors than intracerebellar lesions, a conclusion which we support.

*Tendon Reflexes.* In our records, tendon reflexes showed a remarkable variation, a feature of cerebellar disease which has been noted by others.[5,6,15,27] Holmes[13] emphasized the significance of the pendulous tendon reflex. This was infrequently observed in the patients of this series. Our findings correspond to those of Cushing's who noted dampening of the deep reflexes until the intracranial pressure increased with internal hydrocephalus and there was direct compression of the brain stem involving the pyramidal tract. We believe with others that in cases of tumor of the cerebellum, the reflexes have little localizing value.

Cranial nerve palsies were frequent and, in a number of instances, confused the diagnosis. A paralysis of the third nerve was observed in 11 cases. The syndrome of the cerebello-pontine angle was clear-cut in 4 cases. Complete or incomplete involvement of the third,

fourth, fifth, sixth, seventh and eighth cranial nerves was frequent. Holmes[13] stated that true ocular palsies never result from lesions limited to the cerebellum. Thus, again there is evidence to show the rôle of increased intracranial pressure in producing false signs leading to error in diagnosis or management.

**Summary.** A review has been made of 158 cases of tumor of the cerebellum from the standpoint of unusual symptomatology and findings. The analysis was undertaken in order to clarify the obscure type of case by an understanding of false localizing signs which occur with increased intracranial pressure.

Attention was directed to the occurrence of convulsions and visual field defects which were found to occur in patients with tumor of the cerebellum.

Ophthalmologic findings, spinal fluid pressure, Roentgen findings, sensation, caloric examination results, cranial nerve involvement and tendon reflexes were briefly discussed.

The usual findings in cases of cerebellar tumor were charted.

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# CEREBROSPINAL FLUID PROTEIN VALUES DETERMINED BY TYROSINE EQUIVALENT METHOD.

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The determination of spinal fluid proteins has not kept abreast with the accuracy generally achieved in clinical chemistry. The old method of adding a protein precipitant to the spinal fluid and comparing the resulting cloudiness with turbidity standards has long been recognized as grossly inaccurate. Recently these errors have been subjected to analysis.[3] At best, even the values found to fall in the lowest ranges have been only poor guesses. Protein values for pathologic fluids obtained by mere comparison of turbidity are always subject to uncertainty. Varying concentrations of other constituents affect the quality of the precipitate, therefore, the light absorption, transmission, reflection and dispersion.

Several investigators using the Dennis-Ayer method have claimed that the use of a colorimeter appreciably reduces the errors of this turbidity method. A claim of agreement within 12 mg. per 100 cc. between this method and Kjeldahl methods has been made.[1] This still leaves a high percentage of error when it is considered that often the total protein value is not twice that figure. The work of Merritt and Fremont-Smith,[4] undoubtedly the most comprehensive in the literature, outlines in detail a modification of the Dennis-Ayer method; and the conclusions listed are based mainly on determinations performed by that method. At about the time this mongraph appeared, Johnston and Gibson[2] published a procedure which is highly accurate and practical for the determination of spinal fluid protein. These workers modified the method which employs the Folin-Ciocalteu phenol reagent to determine the tyrosine equivalent of the protein present, and in their publication gave a graph showing the distribution of 500 spinal fluid protein values done routinely for the Department of Neurology.

When we began using the Johnston and Gibson modification in this laboratory we were asked to give the normal range for the method. In the course of determination of this range we also collected data on many pathologic fluids. There is an absence in the literature of data on either the normal or pathologic values for cerebrospinal fluid proteins by this method. We, therefore, present our findings in both instances.

**Method and Material.**—The method used for determination of spinal fluid protein was that described by Johnston and Gibson.[2] All fluids were drawn and stored under sterile conditions. Analyses were performed on the fresh specimens, with the exception of about 150 samples which were aged

about 2 days. This period of aging for sterile fluids was proved to have no effect on the protein value. Specimens were obtained by lumbar puncture. Some fluids from patients with cord tumors came from different levels. About 250 analyses were performed by the Department of Pathological Chemistry, State University of Iowa, on fluids from the University Hospital. Of the specimens analyzed in our laboratory 200 were furnished by Dr. L. P. Ristine, Mt. Pleasant State Hospital; the remainder were obtained from private patients in the Iowa Lutheran Hospital. Diagnosis in all cases represents concurrence of opinion of two or more staff members at these institutions. When a diagnosis of more than one pathologic condition was made, the condition probably having the greatest effect on the protein was selected for classification.

**Discussion.** The findings on spinal fluids from 100 persons diagnosed as normal are summarized in Table 1.

TABLE 1.—SPINAL FLUID PROTEIN VALUES FOR NORMAL PERSONS.

Diagnosis: Normal.
Age: Eight months to 72 years.
Number of cases: 100 (male and female).
Spinal fluid protein: Average, 31.6 mg. per 100 cc. Range, 15.4 to 46 mg. per 100 cc.
Distribution:
6% of the cases had a protein concentration less than 20 mg. per 100 cc.
37% had 20 to 29.9 mg. per 100 cc.
37% had 30 to 39.9 mg. per 100 cc.
20% had greater than 40 mg. per 100 cc.

The occurrence of three values between 45.0 mg. per 100 cc. and 46.0 mg. per 100 cc. pretty well fixes the upper limit of normal for this series at 46.0 mg. per 100 cc. Because of the wide margin of error in preëxisting methods, values heretofore were usually given in multiples of five.

A scatter diagram was made for spinal fluid values against the ages of the subjects. The only order recognizable in this table was the occurrence of ages under 1 year in the region of protein concentrations less than 20 mg. per 100 cc. Concentrations in fluids from persons over 60 years of age had a tendency to be high. The three highest normal values, however, were from persons 30 to 40 years of age.

The protein values which may be expected in pathologic conditions are indicated in Table 2.

In many instances it may appear that there are not sufficient cases to draw valid conclusions about the range or average value. Nevertheless, the conclusions indicated by these cases coincide sufficiently well with the extensive work of Merritt and Fremont-Smith[4] to warrant the publication without further accumulation of data.

To determine what relation the normal average protein value of 31.6 mg. per 100 cc. for both sexes bore to the average for each sex the figures were averaged separately. Seventy per cent of the 100 cases were males with an average protein value of 32.6 mg. per 100 cc; 30% females with a corresponding value of 27.5 mg. per 100 cc.

That body dehydration has little effect on spinal fluid protein concentration is shown in Table 3.

TABLE 2.—SPINAL FLUID PROTEIN VALUES IN VARIOUS PATHOLOGIC CONDITIONS.

| Diagnosis. | No. of cases. | Protein concentration. Average (mg. per 100 cc.). | Protein concentration. Range (mg. per 100 cc.). | No. of cases above 46 mg. per 100 cc. |
|---|---|---|---|---|
| *Organic psychoses with:* | | | | |
| Senility | 14 | 49.9 | 23.6–203.0 | 4 |
| Alzheimer's disease (autopsy) | 2 | 53.9 | 44.5–63.4 | |
| Cerebral arteriosclerosis | 17 | 37.9 | 23.0–64.8 | 4 |
| Neurolues (all types) | 40 | 56.8 | 11.0–156.0 | 21 |
| Brain tumor | 20 | 119.3 | 14.0–540.0 | |
| Brain abscess | 3 | 492.0 | 51.0–877.0 | |
| Cerebral embolism | 16 | 47.6 | 24.0–91.0 | 6 |
| Cord tumor | 10 | 139.1 | 14.0–538.0 | |
| Syringomyelia | 2 | 128.0 | 57.0–199.0 | |
| Paralysis agitans | 2 | 24.5 | 24.0–25.0 | |
| Multiple sclerosis | 20 | 39.8 | 17.0–77.0 | 5 |
| Meningitis | 9 | 258.7 | 19.0–912.0 | |
| Myelitis | 7 | 78.6 | 27.0–216.0 | |
| Encephalomyelitis | 8 | 148.0 | 26.0–272.0 | |
| Poliomyelitis | 3 | 80.0 | 37.5–163.0 | |
| Infectious polyneuritis | 3 | 57.4 | 52.0–63.3 | |
| Encephalitis: | | | | |
| Traumatic | 2 | 40.0 | 36.0–44.0 | |
| Epidemic | 2 | 53.0 | 49.0–57.0 | |
| Chronic | 14 | 47.2 | 16.0–221.0 | 3 |
| Chronic alcoholism | 4 | 57.9 | 47.5–75.0 | |
| Acute alcoholism | 7 | 40.1 | 27.7–48.8 | |
| Drug addiction | 3 | 39.5 | 26.0–47.2 | |
| Neuritis and alcoholic neuritis | 17 | 56.7 | 22.0–122.0 | 8 |
| Neuralgia | 10 | 35.5 | 28.0–52.0 | 1 |
| Migraine | 3 | 25.0 | 24.0–26.0 | |
| Hypertension | 5 | 32.8 | 24.0–37.0 | |
| Pernicious anemia | 3 | 36.3 | 35.0–39.0 | |
| Miscellaneous organic diseases | 5 | 42.2 | 28.5–55.0 | |
| *Functional psychoses:* | | | | |
| Manic depressive (all types) | 17 | 33.0 | 17.0–71.0 | 3 |
| Involutional melancholia | 11 | 38.9 | 24.1–47.0 | 2 |
| Dementia præcox | 28 | 34.7 | 21.0–57.0 | 6 |
| Epileptic | 18 | 36.8 | 23.0–64.0 | 3 |
| Paranoia and paranoid condition | 26 | 31.1 | 17.0–57.0 | 1 |
| Psychoneurosis and neurosis | 27 | 30.0 | 18.0–41.0 | |
| Mental deficiency | 10 | 42.0 | 20.0–114.0 | 4 |
| *Without psychoses:* | | | | |
| Chronic alcoholism | 32 | 34.3 | 19.0–45.7 | |
| Mental deficiency | 8 | 35.4 | 23.0–48.0 | 1 |
| Psychopathic personality | 4 | 36.2 | 28.0–41.0 | |
| Cardiac and gall bladder disease | 5 | 32.6 | 16.0–42.0 | |
| Arthritis of spine | 6 | 45.0 | 31.0–60.0 | |
| No neurol. diagnosis (uremia) | 7 | 55.9 | 47.0–70.0 | |

TABLE 3.—SPINAL FLUID PROTEIN VALUES IN CASES OF DEHYDRATION.

| State of dehydration. | Cases. | Protein concentration. Average (mg. per 100 cc.). | Protein concentration. Range (mg. per 100 cc.). |
|---|---|---|---|
| Moderate | 14 | 34.9 | 27.7–45.2 |
| Extreme | 7 | 35.6 | 22.8–45.2 |

These figures are drawn from cases of psychosis, epilepsy, paranoia, and neurosis having protein values lower than 46.0 gm. per 100 cc. Cases with values above this are worthless for drawing a conclusion in this instance.

**Summary.** 1. Total proteins have been determined by the tyrosine equivalent method on 550 cerebrospinal fluids taken from persons in health and disease.

2. The upper limit of normal values has been found to be 46.0 mg. per 100 cc. The ranges for pathologic values agree well with generally accepted figures in the literature.

3. The average protein values for females is less than that for males.

4. Dehydration does not appreciably affect the protein concentration.

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## NOTE ON A CRETIN'S RESPONSE TO TYPHOID INOCULATION.

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The relation of the endocrine glands to the mechanism and manifestations of the immune state has been discussed for a great many years. In an early book on the endocrines, Bandler[1] (1921) stated that, "The maintenance of the normal state in the various structures of the body is vested in the ductless glands, and immunity, or lack of immunity to various diseases is more than probably one of the most direct evidences of their important function." Mills,[16] in showing the effect of external temperatures on resistance, recently stated that, "Resistance to infection is closely dependent on body combustion level and ease of body heat loss," factors controlled in part by the endocrines. Cannon[7] cites references to hormones as one of the non-specific mechanisms of defense.

Experimental studies have been mainly concerned with the extirpation of specific glands, followed by a study of the immune response of the animals subjected to such procedures. Launoy and

Lévy-Bruhl[15] surveyed the literature to 1915 and saw clearly the confusion, which exists to this day, in experimental work on this subject. For example, they report the work of Fassin and Marbé, who observed a decrease in the immune reaction in thyroidectomized animals, of Lerda and Diez who observed exactly the opposite effect, and of Fjeldstad, who noted no differences in his series of test animals. Launoy and Lévy-Bruhl[15] removed the thyroid (and also the spleen) from chickens and noted no interference with the development of *Spirochæta gallinarum* infections, indicating no increase in immunity. Garibaldi[12] found that the natural heterohemolytic power of the serum of thyroparathyroidectomized dogs is higher than that of normals. Houssay and Sordelli[14] obtained conflicting results following the removal of the thyroid from different animals. They observed a weaker antibody response in the rabbit and horse and an increase in the antibody response of the dog. Parhon and Ballif[17] noted that the removal of the thyroid had an attenuating action on anaphylactic shock in guinea pigs and permitted the animals to survive. This may be taken to indicate a decrease in immune response, rather than an increase. Stschedrowitzky and coworkers[19] noted that the production of antibodies in thyroidectomized animals is considerably weaker after the operation and remained so when tested 6 months later. Haber,[13] in studying the receptivity of rabbits to viruses, noted that thyroidectomy had no effect upon the time of development of encephalitis following infection with herpes virus. M. and A. Derevici[9] noted increased immune reactions following removal of the thyroid from rabbits. The extirpation of the thyroid enhanced the activity of the spleen and is the possible explanation, say these authors, for the increased activity of the immune reactions. They reiterated that thyroid activity is antagonistic to splenic activity. Eickhoff and coworkers[10] found the Arthus phenomenon to be inhibited in sensitized rabbits, following thyroidectomy. Artificial stimulation with thyroid hormone increased the reactions of rabbits in anaphylactic shock. Cope and Kapnick[8] showed that the complement content decreased in the blood of thyroidectomized rabbits, while the response to vaccinia virus of the rabbit is not altered by the operation or by injected thyroxin. In addition, they noted that alterations in complement concentration are not related to the cevitamic acid level in the blood.

The relationship of thyroid function to immunity in the human has not been discussed extensively. For a number of years, we have been interested (from a clinical point of view) in the incidence of various infections in our thyroid-deficient children before and after therapy. No definite conclusions have been drawn. We were able to study a 22-year-old cretin, who had not been treated with thyroid and who was available for immunologic experiments.

**Case Report.** F. D., a 22-year-old white male, a typical sporadic cretin, entered our institution on March 22, 1940, and remained 134 days, until

August 1, 1940. He was a full term infant, second born of a normal 9-month pregnancy, with 1 hour labor. The father is Polish, the mother American born, but of Polish descent. There are 6 other living children, 4 sisters and 2 brothers. The girls and the 8-year-old brother are well at present, but the 13-year-old boy is also a classical hypothyroid. (Familial sporadic thyroid deficiency is a rarity in this country.) When the boy reached the age of 3 years, the mother sought medical advice, because he did not grow and develop like the first child; his skin was very dry, the tongue was large, as were also the head and abdomen. The parent stated that the child stayed in the hospital for 1 year, at the end of which time he sat, walked and ate by himself, all of which he could not do before. From the age of 4 until the present time, the boy's condition was neglected.

Upon entrance, F. D. weighed 46 pounds and was 38½ inches tall, the development being about that of a 7- to 9-year-old. He spoke only in monosyllables,[18] carried out a few simple commands, and had an intelligence quotient of a 3-year-old child.[4-6] The dwarfed stature and mental inadequacy, in addition to supraclavicular fat pads, macroglossia,[5] large abdomen and dry skin readily identified him.

Roentgenograms of the bones revealed marked retardation of skeletal growth, with fragmentation and stippling of the epiphyses of the humeri and femori. The ossification at the wrist corresponded to that of a 6-year-old. Mixed dentition of the permanent and deciduous teeth was present.[11] The films of the heart revealed a cardiac enlargement which was also found on percussion and the electrocardiograph showed low voltage in all levels.[3] The systolic blood pressure was 118 and the diastolic 80.

The initial blood cholesterol was 534 and then fell to normal upon administration of thyroid extract.[2,a,b] Basal metabolic determinations were impossible because of lack of coöperation. Urine and spinal fluid chemical examinations were entirely negative. The Schick and Dick tests were negative upon entrance.

Complete blood count: Hemoglobin, 11.5 gm.; erythrocyte count, 4,250,000; white blood cell count, 6200; myeloid-erythroid ratio, 6%.

Differentials: Neutrophils, 48%; lymphocytes, 30%; stab cells, 13%; mononuclears, 13%.

Blood Kahn and Wassermann tests and spinal fluid Wassermann tests were negative.

Cevitamic acid determination, 1.75 mg. per 100 cc. blood.

Liver function test: Intravenous bromsulphalein, 40% dye in 5 minutes; 0% dye in 30 minutes.

| | At entrance. | After thyroid therapy. |
|---|---|---|
| Blood serum calcium | 8.76 | 9.1 |
| Blood serum phosphorus | 4.62 | 4.4 |
| Blood serum phosphatase | 2.50 | 6.9 |

*Experimental Study.* We studied the patient's response to typhoid vaccine. An agglutination test performed April 20 was negative. The patient received 0.5 cc. of stock typhoid vaccine April 23, and 0.75 cc. April 30. An agglutination test was performed May 2 and was negative. The patient received 1 cc. of stock typhoid vaccine May 7. Agglutination tests performed May 9 and May 13 were negative. The test was again negative on June 20, when thyroid extract therapy was started, ½ grain daily. The dose was increased June 28 to 1 grain daily. An agglutination test performed that day showed partial agglutination, 1 to 80 dilution. The clumps were readily dispersed. The dose of thyroid extract was increased to 2 grains daily and was maintained after

the patient left the hospital. He has been seen regularly since that time and has greatly improved physically. On February 1, 1941, an agglutination test showed a strong positive titer of 1 to 80. The clumps could not be dispersed.

The phagocytic activity of the patient's cells for staphylococci and streptococci were studied and were found to be identical with the normal controls. No attempt was made to immunize the patient to these organisms. No change in phagocytic activity was found after the administration of thyroid extract. Normal adults before and after prolonged administration of thyroid extract showed no variations in phagocytic activity.

**Conclusion.** It appears that the patient showed no response to typhoid inoculation in the absence of thyroid activity. Following the administration of thyroid extract, antibody response was noted. This would seem to indicate a relationship between thyroid function and immune response.

Further studies of this relationship are indicated.

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## MODIFICATION OF RESISTANCE TO ANOXIA, WITH ESPECIAL REFERENCE TO HIGH ALTITUDE FLYING.*

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A MARKED lowering of the pressure of oxygen in an organ of the body produces temporary impairment of function or permanent

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pathologic damage, depending on whether the tissue cell is sensitive to oxygen-want or relatively insensitive. Thus, complete stoppage of the oxygen supply to the lower limbs by compression of the arteries in the thigh has been maintained for over 1½ hours without impairing the function of the muscles of the legs subsequently. On the other hand, asphyxia of the human brain for 5 minutes may result in intracranial hemorrhage or death. Guinea-pigs die in convulsions after inhaling 100% nitrogen for 50 seconds, which in itself is evidence of the special sensitivity of the brain to asphyxia.

The importance of mild degrees of anoxia in clinical and aviation medicine has been emphasized in the past decade. Patients with congestive heart failure and pulmonary emphysema, who at times show no cyanosis and only a slight lowering of the arterial oxygen saturation (88 to 93%), may be relieved of dyspnea and other symptoms of anoxia by inhalation of oxygen-enriched atmospheres. Local tissue anoxia may be severe in the presence of a normal arterial oxygen saturation, as in occlusion of the coronary and cerebral arteries; other clinical syndromes are being recognized in which oxygen treatment of cell anoxia is of value, such as shock and cardiac pain.

In studying the impairment of mental functioning at altitudes of 12,000 feet, we became impressed with the possible relation between "pilot error" and continuous anoxia at that altitude.[2] Recognition of the fact that emotional control and judgment are adversely affected by exposure to relatively mild degrees of oxygen-want is becoming general. On May 1, 1941, the Civil Aeronautics Board inserted the following amendment in its regulations: "61.743 Oxygen Apparatus and Its Use. No air carrier aircraft shall be operated in scheduled air transportation at an altitude exceeding 10,000 feet above sea level continuously for more than 30 minutes, or at an altitude exceeding 12,000 feet above sea level for any length of time, unless such aircraft is equipped with an effective oxygen apparatus and an adequate supply of oxygen available for the convenient use of the operating crew and proper use is made of such apparatus."

In the present world emergency, military flying has been conducted at altitudes so high that anoxia occurs, even with the inhalation of 100% oxygen. The effect of increasing altitude on the alveolar oxygen pressure even in the presence of 100% oxygen is illustrated in Chart 1. The uppermost rectangle schematically represents the proportions of water vapor, $CO_2$ and oxygen in the alveolar air at sea level. The blank white space contains nitrogen and the rare gases. The oxygen molecules are represented by 10 black circles, illustrating an alveolar oxygen pressure of 103 mm. Hg. The next rectangle shows the increased number of oxygen molecules in the lung at sea level when 100% oxygen is inhaled. The alveolar oxygen pressure under these circumstances is 673 mm. Hg. When

the atmospheric pressure is reduced one-half, which occurs at an altitude of 18,000 feet, the original volume of air in the lungs has been expanded to twice the volume present at atmospheric pressure. At 33,700 feet it will be observed that the same number of oxygen molecules is present in the space which represents the lung air as was present in the air breathed at sea level, namely 10 black circles, representing 103 mm. Hg alveolar oxygen pressure. However, at 42,200 feet the volume of air in the lungs has been expanded to six times that present at sea level and the 5 black circles in the lung space now indicate an alveolar oxygen pressure of approximately 50 mm. Hg. It will be observed that the sum of water vapor and carbon dioxide occupy a proportionately larger percentage of the lung space at this high altitude. The pressure of $CO_2$ in the lung air is altered by the degree of hyperventilation.

Chart 1.—Fall in Alveolar Oxygen Pressure With Increasing Altitude.

Since pressure cabins are not usually employed for altitudes of 40,000 feet, at which pilots have already flown during this war, it seemed of interest to study the circumstances which might increase or decrease the fitness of the individual in respect to resistance to acute oxygen-want. These factors may also play a rôle in certain disease conditions discussed above, in which latent or overt anoxia is present.

The first part of this paper illustrates a factor which aggravates the effects of anoxia, namely carbon monoxide poisoning as result of inhaling tobacco smoke. The second part deals with the increase in resistance to oxygen-want at high altitudes after total thyroidectomy.

The smoke from cigarettes yields approximately 1% carbon monoxide by volume, from pipe tobacco about 2%, and cigars about 6% carbon monoxide. Investigators have differed in their estimation of the importance of carbon monoxide poisoning as result of smoking; some consider it negligible whereas others believe that dangerous symptoms may result. Jones and his associates[4]

have reported 5% CO in the blood of persons in a smoke-filled room, and Partridge[3] asserts that there may be 6% saturation in the blood of a moderate cigarette smoker. Since little or no absorption of carbon monoxide takes place from the mouth, the depth of inhaling and the length of time in which the inhaled puff is kept in the lungs are factors which cause variations in the results. We have made various investigations in 30 subjects but in this communication propose to summarize the results of 18 medical students who smoked 20 cigarettes from the time of arising to 3.30 P.M. when blood was drawn for the determination of carbon monoxide and the oxygen capacity. They were all individuals who considered themselves inhaling smokers and were specifically asked to inhale. The methods of analysis were those of Van Slyke.[7]

CHART 2.—EFFECT OF INHALING SMOKING OF 20 CIGARETTES.

| Case No. | CO saturation arterial blood, per cent. | Remarks. |
|---|---|---|
| 1 | 2.2 | Lowest result |
| 18 | 12.3 | Highest result |
| Average (18 cases) | 5.7 | |

The results are summarized in Chart 2 in which it will be seen that the lowest saturation of the blood with CO was 2.2% and the highest 12.3%, the average being 5.7%. Approximately one-half of the subjects tested had a carbon monoxide saturation of between 5 and 10% after smoking 20 cigarettes with inhaling. The effect of CO in displacing oxygen from the hemoglobin becomes less as the blood is subjected to a lower oxygen tension (Peters and Van Slyke).[5] In an interesting study by Asmussen and Chiodi[1] it was shown that the ventilation and circulation are not stimulated by severe CO poisoning, as in hypoöxemia due to breathing lowered oxygen concentrations, but that an acute lowering of the oxygen pressure in the tissues of the brain and heart and other organs takes place, at least partly due to failure of the compensatory stroke volume of the heart.

When a decreased saturation of the arterial blood with oxygen is present, such as at altitudes of 10,000 to 12,000 feet, when the pilot is not breathing oxygen, a saturation of hemoglobin between 6 and 10% with carbon monoxide will aggravate oxygen-want in the tissues. This would also be true at altitudes above 33,700 feet, even though the pilot was inhaling 100% oxygen, since anoxia is present under these conditions, as seen in Table 1. Further studies are in progress to determine to what extent the oxygen tension of the tissues will be lowered by carbon monoxide saturation of the hemoglobin between 6 and 10%.

The second factor to be presented in this paper is the effect of thyroidectomy on resistance to severe anoxia. In 1918 Streuhli[6] reported that thyroidectomized rats were less dyspneic and showed

fewer signs of collapse when exposed to low barometric pressures, as compared to normal animals. He further showed that splenectomy decreased the tolerance to anoxia and that it also nullified the beneficial effects of thyroidectomy.

TABLE 1.—SURVIVAL OF THYROIDECTOMIZED AND NORMAL RATS EXPOSED TO LOW BAROMETRIC PRESSURES FOR 2 HOURS.

| Barometric pressure MM. | Equivalent altitude feet | Normals. | | | Thyroidectomized. | | |
|---|---|---|---|---|---|---|---|
| | | Sur. | Died. | % mort. | Sur. | Died. | % mort. |
| 226 | 30,000 | 5 | 0 | 0 | 5 | 0 | 0 |
| 206 | 32,000 | 9 | 1 | 10 | 5 | 0 | 0 |
| 187 | 34,000 | 6 | 4 | 40 | 5 | 0 | 0 |
| 170 | 36,000 | 1 | 10 | 91 | 5 | 0 | 0 |
| 155 | 38,000 | 0 | 5 | 100 | 6 | 0 | 0 |
| 141 | 40,000 | 0 | 5 | 100 | 5 | 1 | 17 |
| 128 | 42,000 | 0 | 5 | 100 | 4 | 1 | 20 |
| 111 | 44,000 | 0 | 5 | 100 | 3 | 1 | 25 |
| 105 | 46,000 | 0 | 5 | 100 | 0 | 3 | 100 |

We studied the effect of thyroidectomy on mortality in rats exposed to low barometric pressures, as well as to low oxygen concentrations. The accompanying table shows the mortality after a 2-hour exposure to various barometric pressures. It will be seen that the difference between the normal and the thyroidectomy group is indeed remarkable. Normal animals die at an altitude of 34,000 feet whereas the thyroidectomy group is alive up to an altitude of 42,000 feet. In chamber experiments about 75% of 30 thyroidectomized rats survived a 3-week exposure to 6% oxygen whereas 80% of a similar number of normal rats were dead within a period of 12 to 36 hours.

The importance of these observations will depend upon the extent to which they may be made applicable to flying conditions. It seems likely that pilots whose basal metabolism is 20% above normal would withstand very high altitudes less well than pilots whose basal metabolism is 20% below normal. Furthermore, measures may be found which will make possible a temporary lowering of the oxygen consumption. The physiologic explanation of these results in thyroidectomized animals would appear to lie in a higher oxygen tension in the tissues of the operated animals, as result of a far lower consumption of oxygen in the individual cells.

**Conclusion.** Carbon monoxide poisoning as a result of inhaling tobacco smoke may under certain circumstances become a factor which impairs resistance to anoxia, especially when the pilot is traveling without oxygen at altitudes of 10,000 to 12,000 feet, and also in the presence of 100% oxygen at altitudes between 34,000 and 40,000 feet. In 18 inhaling smokers, the average CO saturation of arterial blood was 5.7% after smoking 20 cigarettes from 9 A.M. to 4 P.M. Nine of the subjects had a carbon monoxide saturation between 5 and 10%.

Rats who have been thyroidectomized show a remarkable increase

in resistance to very high altitudes. Normal rats die at 34,000 feet in a 2-hour period, whereas thyroidectomized animals survive at barometric pressures which correspond to an elevation of 42,000 feet. The majority of thyroidectomized rats survive 3 weeks in a chamber kept at 6% oxygen whereas a similar percentage of normal rats die in 12 to 36 hours' exposure to this low oxygen concentration.

Additional studies are in progress to determine the significance of this degree of carbon monoxide poisoning as a result of inhaling tobacco smoke from cigarettes. The importance of variations in oxygen consumption is also being additionally studied in subjects exposed to low barometric pressures.

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## STERNAL MARROW CHANGES DURING THE FIRST WEEK OF LIFE.

### CORRELATION WITH PERIPHERAL BLOOD FINDINGS.

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THE sternal aspiration method of studying bone marrow is one which permits repeated examinations at short intervals of time. It was felt that this procedure might thus be used to advantage in an attempt to explain certain well-known hematologic changes which occur in the peripheral blood during the neonatal period.

At the time of birth, the blood of the normal infant* has a high content of red cells and hemoglobin and an elevated reticulocyte count, with a fall in red cells and hemoglobin soon after birth[2,3,7,9,12,22,24,25,33,38,42,48,49a,50,51,53,58,59,65–67,75a,b,76–78] The accepted explanation for these findings is that the change from low to high oxygen tension makes unnecessary in the newborn the large number of red cells which was required in the fetus.[3,10,20,21,29a–c,30,34,35,37,44,47,52,67,75a,b,79] Thus, a breakdown of redundant red cells takes place.

* The infants studied were in the newborn nursery of the Jewish Maternity Hospital.

The destruction of these red cells is generally believed to be due to some marked hemolytic process occurring in the blood stream. However, this idea of excessive hemolysis might be questioned in view of the sharp drop in reticulocyte percentage during the first week of life.[7,15,24,27,29a,b,39a,b,41a,51,63,76,78]

Along with the high red cell, hemoglobin, and reticulocyte levels at birth, there is also a high white cell count, which similarly has been attributed to hemopoietic hyperfunction caused by requirements of fetal existence.[7] But how can one explain the leukocyte changes during the first week,[6–9,12,14,26,39b,47,48,58,65,78] at which time the white cell count decreases and the blood picture at birth becomes one of lymphocytic predominance?

The present study was undertaken with the hope of advancing hematologic knowledge of the newborn period. By means of sternal puncture, we have sought to determine whether there was any correlation between the bone marrow picture and the peripheral blood, and whether the findings could point the way to a possible explanation for the changing blood picture in the neonatal period.

Since Arinkin's[4a] introduction of the sternal aspiration method in 1927, there have been many reports of the sternal puncture findings in infants and children;[16–19,23,28,31,40a,b,41b,43,46,60,64,72,74] but in only 3 of these has the method been described in detail. All used cut down lumbar puncture needles. Kato[41b] used a needle 4 cm. long, and Diwany[19] a needle cut short and fitted with a movable shield which could be fixed at any required distance; Vogel and Bassen[74] used an 18-gauge, ½-inch (1.27 cm.) needle, but mentioned that a 20-gauge, ¼-inch (0.64 cm.) needle was preferable in infants under 1 year. The method to be reported here utilizes this ¼-inch needle (Fig. 1). The procedure is simple and can be performed with safety and accuracy.

**The Study.** Blood counts and sternal marrow aspirations were done on 35 normal full-term infants (14 males, 21 females) in the first 24 hours of life and again 1 week later. The youngest was 2 hours old and the oldest was 23 hours at the time of the first examination.

Examination of peripheral blood, taken from the big toe, consisted of RBC count, hemoglobin determination, WBC count, differential, and reticulocyte count.*

The materials used in the sternal marrow aspiration were: 1, A dry sterile ¼-inch, 20-gauge lumbar puncture needle. 2, A dry sterile 20-cc. glass syringe (Luer type). 3, Iodine and alcohol. 4, Sterile cotton balls and gauze pads. 5, White blood cell pipette. 6, White blood cell diluting fluid (2% acetic acid solution). 7, Clean glass slides.

* The diluent used in counting the RBC was Hayem's solution; 2% acetic acid solution was used in the WBC count (a correction was made for nucleated RBC). The Hb was determined by the method of Sahli (100% = 14.5 gm.).

The WBC differential was made by staining the spreads with Jenner and Giemsa stains and counting 100 cells.

The reticulocyte per cent was determined by counting 1000 erythrocytes in a spread stained by a 1% alcoholic solution of brilliant cresyl blue and then by Jenner and Giemsa stains.

The advantages of using a short needle are: 1, There is no fear of dangerous penetration into the chest cavity, for the hilt of the needle acts as a guard. 2, A small amount of material may be obtained without the possibility of admixture with peripheral blood. 3, Once the needle has penetrated into the marrow cavity it can be held firmly in position.

*Technique.* 1. The arms were immobilized at the sides and a pad was placed behind the shoulders in order to throw the head back. A nurse held the infant's head in this position.

2. The skin of the upper sternum was prepared with iodine and alcohol. No anesthesia was used.

FIG. 1.—A 20-gauge lumbar puncture needle cut down to ¾ inch length.

3. The needle was inserted at the midline into the manubrium. This site was found to be best suited for puncture in infants because its slightly greater thickness permitted the needle to be well fixed in position. The needle was directed cephalad at an angle of about 45 degrees.*

4. The trocar was removed and the syringe was attached to the needle. Suction was applied until the marrow material appeared in the neck of the syringe. If at first no material was obtained the trocar was reinserted and the needle rotated *in situ*. If this also failed, as occasionally happened, the needle was withdrawn completely and reinserted in a nearby spot.

5. The needle and syringe were withdrawn and an alcohol sponge applied with gentle pressure to the puncture wound.

6. The contents of the syringe were expressed on a glass slide. From this a count was made of the nucleated cells, including the megakaryocytes, and smears were spread. These were stained with Jenner and Giemsa stains, 500 cells being counted in the differential.

* In infants and young children there is complete absence of the sudden give, so characteristic in the adolescent and adult when the needle penetrates through the hard outer bony shell into the marrow space.

TABLE 1.—INDIVIDUAL PERIPHERAL BLOOD AND MARROW COUNTS IN FIRST 24 HOURS AND 1 WEEK LATER.

| Number. | Sex. | Age (hrs.). | Weight (lbs. and oz.). | Peripheral Blood. | | | | | | | | | | | | | | Bone Marrow. | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Hb. | | | | | Differential. | | | | | | | | Feeding. | Chamber count. | | Differential. | | | | | | | | | | | | | | | | |
| | | | | % | Gm. | RBC (millions). | Reticulocyte, %. | WBC (thousands). | Myelocyte. | Non-segmented neutrophil. | Segmented neutrophil. | Eosinophil. | Basophil. | Lymphocyte. | Monocyte. | Normoblasts 100 WBC. | | Nucleated red and white cells (thousands). | Megakaryocytes. | Myeloblast. | Myelocyte neutrophil. | Eo. myelocyte. | Non-segmented neutrophil. | Segmented neutrophil. | Eosinophil. | Basophil. | Lymphocyte. | Hematogone. | Megakaryocyte. | Reticulum cell. | Megaloblast. | Erythroblast. | Normoblast. | Total nucleated RBC. |
| 1 | F | 2 | 6:14 | 140 | 20.5 | 5.96 | 2.4 | 23.2 | 1 | 13 | 53 | | | 26 | 7 | 1 | Br. | 358 | 44 | 0.2 | 16.0 | 0.2 | 40.0 | 8.0 | 1.6 | | 0.4 | 5.8 | | | | 0.6 | 27.2 | 27.8 |
| | | | | | | | | | | | | | | | | | | 63 | 44 | 1.0 | 19.0 | | 42.0 | 22.0 | 0.2 | | 4.2 | 4.2 | | | | | 7.4 | 7.4 |
| | | | 6:7½ | 108 | 15.7 | 4.62 | 0.2 | 17.0 | | | 54 | 2 | | 36 | 8 | | | 172 | 264 | | 9.0 | 0.4 | 46.0 | 11.0 | 1.4 | | 1.4 | 5.4 | | | | 1.0 | 25.2 | 26.2 |
| 2 | F | 3 | 7:6 | 150 | 22.0 | 6.04 | 1.9 | 19.7 | | 18 | 67 | 1 | | 11 | 3 | 1 | Br. | 213 | 66 | 3.4 | 19.0 | 0.8 | 48.8 | 7.0 | 1.8 | | 4.4 | 4.4 | | | | | 10.4 | 10.4 |
| | | | 7:8 | 144 | 21.1 | 5.02 | 0.3 | 10.0 | | | 20 | | | 67 | 13 | | | 213 | 66 | | 22.0 | 1.0 | 42.2 | 4.0 | 1.8 | | 0.8 | 0.4 | | | 0.2 | 1.0 | 26.6 | 27.8 |
| 3 | F | 4¼ | 6:15 | 154 | 22.6 | 6.94 | 1.4 | 43.3 | 2 | 11 | 60 | 2 | | 22 | 3 | 1 | Br. | 280 | 22 | | 14.8 | 1.2 | 54.0 | 13.0 | 2.6 | 0.2 | 6.0 | 1.6 | | 0.6 | | 0.8 | 5.0 | 5.8 |
| | | | 6:11 | 130 | 19.0 | 5.26 | 0.1 | 14.0 | | 1 | 38 | 1 | | 56 | 4 | | | 125 | 22 | 0.2 | 16.4 | 0.6 | 21.2 | 10.4 | 0.6 | | 0.2 | 1.0 | | 0.4 | 1.0 | 3.4 | 44.6 | 49.0 |
| 4 | F | 4¼ | 6:15 | 132 | 19.3 | 7.15 | 1.8 | 20.7 | 1 | 11 | 71 | 1 | 1 | 11 | 4 | 1 | Br. | 322 | 110 | 0.2 | 16.4 | 0.6 | 21.2 | 10.4 | 0.6 | | 1.0 | 2.2 | 0.2 | 0.6 | 0.2 | 0.4 | 11.4 | 12.0 |
| | | | 7:2 | 112 | 16.3 | 4.85 | 0.2 | 12.1 | | 4 | 29 | | | 64 | 3 | | | 83 | 66 | 2.4 | 16.8 | 0.2 | 34.2 | 29.4 | 1.0 | | 1.0 | 2.2 | 0.2 | 0.6 | 0.2 | 0.4 | 11.4 | 12.0 |
| 5 | F | 5¼ | 7:6 | 166 | 24.4 | 5.79 | 1.3 | 34.9 | 3 | 21 | 52 | 2 | | 21 | 1 | | Br. | 127 | 22 | 0.4 | 17.4 | 1.6 | 42.2 | 5.4 | 2.0 | 0.2 | 5.6 | 0.4 | | | 0.2 | 2.6 | 22.0 | 24.8 |
| | | | 7:9 | 144 | 21.1 | 5.07 | 0.1 | 13.6 | 1 | 6 | 18 | 2 | 1 | 60 | 12 | | | 185 | 22 | 1.6 | 15.2 | 0.2 | 61.0 | 4.2 | 0.4 | 0.2 | 7.8 | 1.0 | | | | 0.4 | 8.0 | 8.4 |
| 6 | M | 5¼ | 8:1 | 138 | 20.2 | 6.09 | 1.4 | 22.8 | | 19 | 62 | | 1 | 13 | 5 | | Br. | 166 | | 1.4 | 6.4 | | 42.6 | 3.8 | 3.0 | | 4.4 | 5.4 | | | | 0.2 | 32.8 | 33.0 |
| | | | 8:2 | 118 | 17.2 | 5.29 | 0.2 | 12.1 | | 8 | 41 | 3 | | 41 | 7 | | | 91 | 22 | 1.2 | 28.0 | 0.6 | 42.6 | 5.0 | 1.2 | | 2.4 | 4.0 | | | | | 15.0 | 15.0 |
| 7 | M | 5¼ | 6:11 | 128 | 18.7 | 5.33 | 1.1 | 35.0 | 1 | 13 | 72 | | | 13 | 1 | 1 | Br. | 271 | 22 | 1.6 | 16.2 | 0.2 | 41.0 | 7.0 | 1.8 | | 1.2 | 6.0 | | | | 0.8 | 24.2 | 25.0 |
| | | | 6:11 | 128 | 18.7 | 4.89 | 0.1 | 13.4 | | 1 | 55 | 1 | | 41 | 2 | | | 190 | | 1.6 | 34.0 | 0.2 | 36.0 | 10.0 | 0.4 | | 1.0 | 7.0 | 0.2 | | | 1.0 | 8.6 | 9.6 |
| 8 | F | 6 | 6:7 | 110 | 16.0 | 5.99 | 2.5 | 25.7 | 1 | 12 | 57 | 1 | | 26 | 3 | 1 | F. | 123 | 110 | 0.8 | 13.2 | 1.2 | 31.8 | 9.0 | 4.6 | | 7.2 | 1.4 | | | | 1.4 | 29.4 | 30.8 |
| | | | 6:11 | 90 | 13.0 | 4.75 | 0.6 | 9.4 | | 4 | 33 | 1 | | 54 | 8 | | | QNS | † | 1.0 | 24.0 | 1.0 | 44.8 | 9.0 | 1.8 | | 2.6 | 6.8 | | | | 0.4 | 8.6 | 9.0 |
| 9 | M | 6¼ | 8:15 | 120 | 17.5 | 5.49 | 4.0 | 29.6 | 1 | 22 | 51 | 1 | | 17 | 8 | | Br. | 245 | | | 13.6 | 0.2 | 37.4 | 6.6 | 3.4 | | 1.0 | | | 0.6 | | 37.2 | 37.8 |
| | | | 9:0 | 116 | 16.9 | 4.89 | 0.4 | 18.9 | | 3 | 39 | 1 | | 52 | 5 | | | 239 | 66 | | 16.0 | | 56.4 | 11.6 | 2.8 | | 0.8 | 0.8 | | | | 0.6 | 11.0 | 11.6 |
| 10 | M | 6¼ | 8:8 | 108 | 15.7 | 4.75 | 1.1 | 18.4 | | 5 | 42 | 1 | 1 | 44 | 7 | 5 | Br. | 190 | 22 | 0.8 | 16.8 | | 31.0 | 5.0 | 0.6 | | 4.2 | 5.2 | | | | 1.4 | 35.0 | 36.4 |
| | | | 8:15 | 102 | 14.8 | 4.64 | 0.4 | 9.9 | | | 19 | | 1 | 70 | 10 | | | 145 | 66 | 0.6 | 19.0 | | 38.0 | 8.0 | 1.2 | | 5.2 | 12.4 | 0.2 | | | | 15.4 | 15.4 |
| 11 | M | 6¼ | 6:15 | 142 | 20.8 | 5.91 | 3.0 | 28.8 | 1 | 26 | 40 | 1 | | 23 | 9 | | Br. | 212 | 110 | 0.4 | 24.0 | | 34.2 | 2.0 | 4.0 | | 4.2 | 5.2 | | | | 0.8 | 25.2 | 26.0 |
| | | | 6:15 | 124 | 18.1 | 5.92 | 0.2 | 18.0 | | 1 | 26 | | | 65 | 8 | | | 327 | 220 | 1.4 | 19.0 | 0.4 | 49.0 | 16.4 | 1.4 | | 2.2 | 3.0 | | 0.2 | | | 7.0 | 7.0 |
| 12 | I | 7 | 7:5 | 144 | 21.1 | 5.52 | 4.4 | 13.5 | 1 | 14 | 47 | | | 28 | 10 | | Br. & F. | QNS | | 1.0 | 12.0 | 1.0 | 33.0 | 7.2 | 1.6 | | 1.8 | 1.8 | | | 0.2 | 5.2 | 35.2 | 40.6 |
| | | | 8:1 | 128 | 18.7 | 5.12 | 1.2 | 12.3 | | 2 | 12 | 1 | | 80 | 5 | | | QNS | | 0.6 | 17.0 | 0.8 | 42.0 | 9.2 | 2.8 | | 6.2 | 2.6 | | | 0.2 | 2.6 | 16.0 | 18.8 |
| 13 | F | 7½ | 7:4 | 140 | 20.5 | 4.23 | 1.2 | 33.0 | | 10 | 67 | | | 17 | 6 | 2 | Br. | QNS | | 0.8 | 11.6 | 0.2 | 31.4 | 5.8 | 1.4 | 0.4 | 8.4 | 2.4 | | | 0.2 | 1.2 | 36.2 | 37.6 |
| | | | 7:6 | 132 | 19.3 | 4.17 | 0.2 | 11.4 | | 3 | 27 | 1 | | 65 | 4 | | | 97 | 66 | 0.8 | 15.4 | 1.0 | 48.0 | 10.0 | 0.6 | | 10.2 | 1.2 | | | 0.2 | 1.2 | 11.4 | 12.8 |
| 14 | M | 8½ | 8:7 | 124 | 18.1 | 5.68 | 2.5 | 20.9 | | 17 | 49 | 2 | | 26 | 6 | 2 | Br. | 285 | | 0.6 | 8.0 | | 41.0 | 3.0 | 2.4 | | 1.4 | 3.6 | | | | 1.8 | 38.2 | 40.0 |
| | | | 8:6 | 106 | 15.4 | 4.57 | 0.4 | 11.1 | | | 36 | | | 59 | 5 | | | 88 | 22 | 1.0 | 18.2 | 0.8 | 39.0 | 12.0 | 1.8 | | 7.6 | 6.2 | | | | 0.2 | 13.2 | 13.4 |
| 15 | M | 9½ | 9:7 | 144 | 21.1 | 6.27 | 3.2 | 25.8 | | 18 | 68 | | | 13 | 1 | | Br. & F. | 86 | | 1.4 | 12.8 | 0.6 | 25.0 | 17.0 | 1.4 | | 6.0 | 5.0 | | | 0.4 | 0.4 | 30.0 | 30.8 |

| | | |

*Classification of Bone Marrow Cells.* The nucleated cells in the sternal marrow smears were identified according to the classification of Vogel and Bassen.[74] The cells noted were grouped under the following headings: Myeloblasts; Myelocytes; Eosinophilic myelocytes; Non-segmented neutrophils; Segmented neutrophils; Eosinophils; Basophils; Lymphocytes; Megakaryocytes; Hematogones; Reticulum cells; Nucleated RBC: Megaloblasts, Erythroblasts, Normoblasts.

**Results.** In Table 1 are given the data for the individual infants, arranged according to their age at the time of the first examination. The second line of figures under each number represents the findings 1 week later. Table 2 presents the average findings in the 35 infants studied.

*Age.* At the time of the first examination, the age of the infants varied from 2 to 23 hours (average, 11.4). There were no significant differences according to age in hours during the first day of life.

*Sex.* There were 21 females and 14 males. No important differences existed because of sex.

*Weight.* The weight averaged 7:2 (6:0–9:7) at time of the first examination and 7:5 (5:14–9:12) a week later. We found no relationship between birth weight and height of hemoglobin,[49b] nor were any other noteworthy differences found because of weight.

*Feeding.* As may be noted in Table 1, most of the infants were breast fed, a few were on breast and formula, and a few were on formula exclusively. Consequently, no conclusions could be drawn from this factor. However, it does not seem likely that variations in adequate feeding should be of any consequence.

*Jaundice.* Although jaundice was present in no infant on the 1st or the 8th day, physiologic icterus occurred in 4 of the babies studied. This in nowise affected the hematologic picture.

**Peripheral Blood.** *Hemoglobin.* On the 1st day the Hb varied between 102–172%, averaging 135% (19.8 gm.). A week later it varied between 90–168%, and averaged 121% (17.6 gm.). In some cases, little if any change took place.

*Red Blood Cells.* On the fist day the RBC varied between 4.23–7.15 million (average, 5.53 million). A week later the count dropped to a range of 3.40–6.14 million (average, 4.8 million). In some cases, little if any change took place. It may be noted that in most of these latter cases, moreover, the Hb change was also negligible.

*White Blood Cells.* On the 1st day the corrected WBC count varied from 12,100 to 43,250 (average, 24,000). A week later the count varied from 8350 to 27,650 (average, 14,200).

*Differential.* The myeloid cells dropped from an average of 70% down to 35% at the end of a week, with a shift to the right taking place. The lymphocytes increased from 25% to 59%. There was no significant change in the monocytes.

*Reticulocytes.* On the 1st day the reticulocytes varied between 1–4.7% (average, 2.3%); a week later the range was 0.1–1.2% (average, 0.4%).

**Sternal Marrow.** In a few cases not enough material was aspirated for a chamber count to be done, although spreads were made.

*Nucleated Red and White Cells.* The range was approximately the same on the 1st and 8th day, and although some infants showed an increased count after a week, the average decreased from 186,000 per c.mm. (54,000–358,000) to 134,000 (53,000–327,000). This difference did not seem to be of great importance.

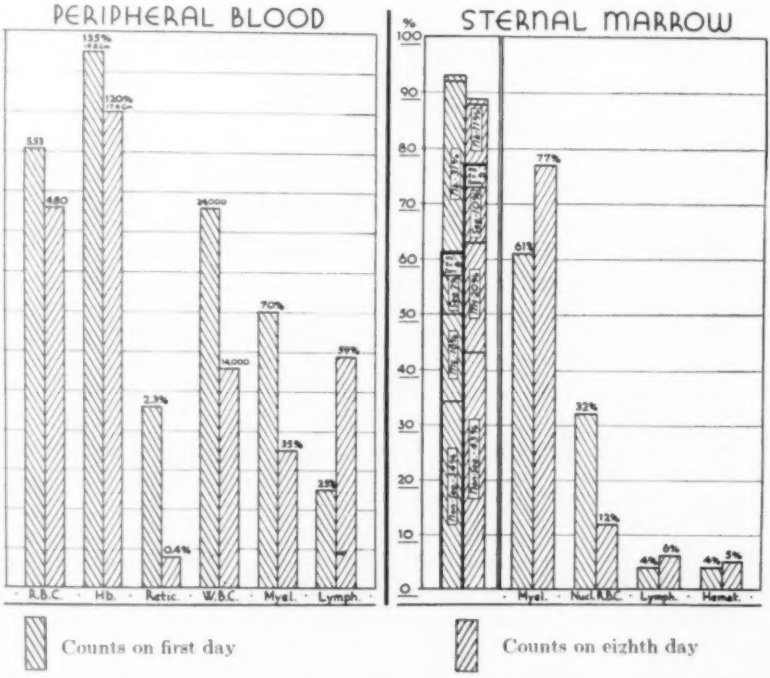


CHART 1.—Peripheral blood and sternal marrow findings on 1st and 8th day. The first two columns under sternal marrow show a comparison between the myeloid cells and the nucleated red cells on the 1st and 8th day. A heavy black line separated these two cell groups. It will be seen that the two groups comprise about 90% of marrow cells on both days. The figures of the 1st day total 101% because round figures were used.

*Megakaryocytes.* On the 1st day the figures varied between 0–264 per c.mm., whereas the range a week later was 0–220. No significant changes took place in this period of time.

*Differential* (Chart 1). The myeloid series and the nucleated red blood cells comprised about 90% of the nucleated cells both on the 1st and the 8th day; lymphocytes and hematogones made up most

of the rest. However, a striking change in relation was noted in every case after a week's time. On the first day of life the percentage of myeloid cells averaged 61% and the nucleated RBC 32% (16.4–49%). On the 8th day the myeloid percentage had increased to 77%, whereas the erythroid elements dropped sharply to 12% (5–23%). Thus, the Myeloid/Erythroid Ratio increased from 1.9 to 6.7. Presented in a slightly different fashion, there were about one-half as many nucleated RBC as myeloid cells on the 1st day but only one-seventh as many on the 8th day.

TABLE 2.—AVERAGE PERIPHERAL BLOOD AND MARROW COUNTS IN FIRST 24 HOURS AND 1 WEEK LATER.

| | All cases. | | Females. | | Males. | |
|---|---|---|---|---|---|---|
| | 1st 24 hrs. | Wk. later. | 1st 24 hrs. | Wk. later. | 1st 24 hrs. | Wk. later. |
| Age in hrs. | 11.4 | | 11.3 | | 11.7 | |
| Wt. (lbs. and oz.) | 7:02 | 7:05 | 7:00 | 7:03 | 7:12 | 7:13 |
| *Peripheral blood chamber count:* | | | | | | |
| Hb., % | 135.1 | 120.6 | 131.6 | 117.1 | 140.4 | 125.7 |
| Hb., gm. per 100 cc. | 19.8 | 17.6 | 19.3 | 17.1 | 20.5 | 18.3 |
| RBC (millions) | 5.5 | 4.8 | 5.4 | 4.7 | 5.7 | 5.0 |
| WBC (thousands) | 24.0 | 14.2 | 24.9 | 14.1 | 23.0 | 14.7 |
| *Peripheral blood smear:* | | | | | | |
| Myelocyte | 0.8 | 0.0 | 0.9 | 0.1 | 0.8 | 0.0 |
| Non-segmented | 13.5 | 2.5 | 12.3 | 2.3 | 15.4 | 2.9 |
| Segmented | 54.6 | 31.5 | 54.5 | 29.0 | 54.6 | 35.1 |
| Eosinophil | 0.9 | 1.1 | 0.9 | 1.3 | 1.1 | 0.7 |
| Basophil | 0.3 | 0.2 | 0.4 | 0.2 | 0.2 | 0.1 |
| Lymphocyte | 24.9 | 58.6 | 26.4 | 60.6 | 22.7 | 55.6 |
| Monocyte | 5.0 | 6.1 | 4.7 | 6.5 | 5.2 | 5.5 |
| N. per 100 WBC | 1.2 | 0.1 | 1.2 | 0.1 | 1.2 | 0.0 |
| Reticulocyte, % | 2.3 | 0.4 | 2.4 | 0.4 | 2.2 | 0.3 |
| *Sternal marrow chamber count:* | | | | | | |
| Nucleated RBC and WBC | 185,843 | 134,200 | 190,375 | 103,526 | 180,714 | 171,583 |
| Megakaryocytes | 58.7 | 82.9 | 74.3 | 62.3 | 40.9 | 105.3 |
| *Sternal marrow smear:* | | | | | | |
| Myeloblast | 0.8 | 1.5 | 0.7 | 1.5 | 1.1 | 1.5 |
| Myelocyte | 16.3 | 19.7 | 17.0 | 18.1 | 15.9 | 22.1 |
| Myelocyte Eo. | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.5 |
| Non-segmented | 33.9 | 43.5 | 36.7 | 45.1 | 29.6 | 41.0 |
| Segmented | 7.0 | 10.4 | 6.8 | 10.4 | 7.2 | 10.5 |
| Eosinophil | 2.0 | 1.7 | 1.9 | 1.7 | 1.6 | 1.6 |
| Basophil | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Lymphocyte | 3.8 | 6.2 | 3.4 | 6.7 | 4.2 | 5.5 |
| Megakaryocyte | 0.1 | 0.1 | 0.1 | 0.1 | 0.0 | 0.1 |
| Hematogone | 3.8 | 4.8 | 3.8 | 5.4 | 3.5 | 3.9 |
| Reticulum | 0.0 | 0.1 | 0.0 | 0.0 | 0.0 | 0.2 |
| Megaloblast | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.0 |
| Erythroblast | 1.0 | 0.5 | 1.1 | 0.5 | 1.0 | 0.5 |
| Normoblast | 30.8 | 11.0 | 28.0 | 10.0 | 35.1 | 12.5 |
| Total nucleated RBC | 31.9 | 11.6 | 29.2 | 10.6 | 36.3 | 13.1 |
| Myeloid/Erythroid ratio | 1.9 | 6.7 | 2.2 | 7.3 | 1.5 | 5.9 |

Examination of the figures for the myeloid cells in Tables 1 and 2 revealed that with few exceptions the non-segmented neutrophils were the most abundant on the 1st day and that they showed the greatest increase at the end of the week. There was also an average increase in the myelocytes and segmented neutrophils.

The lymphocytes and the hematogones each represented about 4% of the nucleated bone marrow cells in the 1st day. The increase by the 8th day was slight.

**Discussion.** *Peripheral Blood.* Comparing our figures with those of others, we note that in general our findings in the peripheral blood agree with those of earlier investigators. Here it is important, not that figures reported by various authors have differed from one another, but that they have indicated the direction of the changes in the blood during the neonatal period.

*Hemoglobin.* It has been established that the high hemoglobin content of the blood diminishes within the first few weeks of life. Regardless of when the greatest drop takes place,[13,22,24,32,42,66] our cases showed a fall from 135% (19.8 gm.) on the 1st day to 121% (17.6 gm.) a week later. Mackay's[49a] figures in the same period of time fell from 19.7 to 17.9 gm., and Sanford's[57] fell from 18.8 to 15.6 gm.

*Red Blood Cells.* Our cases had an average count of 5.53 million on the 1st day. This coincides closely with the figures of Lucas[48] (5.51 million), Mitchell[53] (5.68 million), Faxen[24] (5.78 million), Sanford's[57] (5.8 million), and Slawik[65] (5.85 million). On the 8th day our cases averaged 4.8 million, Lucas'[48] averaged 4.5 million, Sanford[57] averaged 5 million and Faxen's[24] averaged 5.12 million. Wollstein,[78] on the other hand, found the RBC count on the 7th day to be higher than at birth, falling below birth level early in the second week.

*White Blood Cells.* It is universally agreed that the high white cell count at birth falls during the first week of life, the figures varying with different investigators. On the 1st day we found 24,000, Bakwin and Morris[8] reported 20,300, Lippman[47] found 22,500 at 12 hours, and Frank[26] found 29,000 at 12 hours. On the 8th day our cases averaged 14,200, Bakwin and Morris'[8] 10,200, Frank's[26] 10,700.

*Differential.* Here too there is unanimity of opinion, namely, that the large number of myeloid cells at birth becomes reduced, with a shift to the right taking place at the end of the 1st week, at which time the picture also shows lymphocytic predominance. Our figures of 70% myeloid cells on the 1st day and 59% lymphocytes on the 8th day are almost identical with those summarized by Baar and Stransky.[7]

*Reticulocytes.* Of great significance is the drop in reticulocyte percentage which takes place during the 1st week of life. This finding is unquestioned. Our figures dropped from 2.3% in the first 24 hours to 0.4% on the 8th day. For the same period of time, Faxen[24] reported a fall from 2.2% to 0.38%, and Merritt and Davidson[51] found a drop from 3.4% to 0.17%. Krumbhaar's[45] counts, starting at 4.5% 4 hours after birth, dropped to 1.7% at the end of 24 hours and were stabilized at 0.3% by the 10th day. Woll-

stein's[78] figures for the 1st day were 1.2–2.6%, falling below 0.5% by the 10th day.

*Bone Marrow.* Before attempting to compare our study with those of others who have carried on similar investigations in this age group, it would be wise at this point to summarize briefly the essential findings (Chart 1): In the 1st day of life the myeloid cells (61%) and the nucleated RBC (32%) comprised over 90% of the nucleated cells in the sternal marrow. The most abundant single cell type was the non-segmented neutrophil (34%), closely followed by the normoblast (31%), after which came the myelocyte (16%) and the segmented neutrophil (7%).

After a week's time the myeloid cells (77%) and the nucleated RBC (12%) still made up almost 90% of the bone marrow cells, but the former group had increased and the latter had dropped sharply. On the 8th day the non-segmented neutrophil (43%) was still in first place, but the myelocyte (20%) had replaced the normoblast (11%) for second place. The segmented neutrophil followed with 10%.

The small percentage of lymphocytes and hematogones increased but slightly by the end of the 1st week of life.

The work of Tecilazic[69] in 1935, although not strictly comparable because he aspirated tibial marrow, is of great interest. In a small series of cases he compared the marrow picture with the peripheral blood smear. He too found that at birth the myeloid and erythroid elements comprised over 90% of all the nucleated cells; on the 7th day these two groups totalled slightly under 90%. However, in Tecilazic's cases the nucleated RBC (66%) far exceeded the myeloid cells (30%) at birth. On the 7th day he found the relationship to be reversed. Comparing his series with ours, we note:

| | | Myeloid. | Erythroid. | M/E Ratio. |
|---|---|---|---|---|
| Tecilazic . . . . . | 1st day | 30 | 66 | 0.5 |
| | 7th day | 48 | 40 | 1.2 |
| Shapiro and Bassen . . . | 1st day | 61 | 32 | 1.9 |
| | 8th day | 77 | 12 | 6.7 |

Tecilazic stated that during the first week intense regeneration of the granulocytes occurred, especially among the younger forms (non-segmented neutrophils, myelocytes, and myeloblasts), while in the peripheral blood the granulocytes diminished. The author made no attempt to explain his findings, nor did he investigate the changing red cell picture in the peripheral blood.

Lamy and his coworkers reported sternal marrow findings in the newborn in 1935[18] and in 1939.[46] In the earlier paper, devoted chiefly to the bone marrow findings in the adult, they stated that no important differences from the adult myelogram were found in infants over 6 months of age. Figures reported for only 1 infant on the 1st day of life showed 45% nucleated RBC. Further investi-

gations were cited in the later paper. Although no tables of figures were given, several interesting conclusions were reached:

1. At birth and during the first few days there are 35–50% nucleated RBC, the great majority of which are normoblasts. At this time, there is a high percentage of granulocytes, especially of the young forms; and the number of lymphocytes is very slight.

2. In the course of the 1st week, the nucleated RBC fall to 25–35%; the granulocytes increase, especially the segmented neutrophils; and the lymphocytes also increase.

Despite the fact that the percentage of nucleated red cells here given is somewhat higher than our own, the above conclusions are in general agreement with our findings, except that we found, as did Tecilazic, that the greatest increase at the end of the week was among the younger granulocytes and not the segmented neutrophils. In 1938 Veeneklaas[72] reported on the sternal puncture in children, dividing them into various age groups. The investigator felt that Group I, consisting of 3 infants below the age of 14 days, was too small to be of any value statistically. However, it is of interest to note that the average figures for that group are quite similar to our averages for the 8th day.

| | Myeloid. | Erythroid. | M/E Ratio |
|---|---|---|---|
| Veeneklaas | 67 | 12 | 5.6 |
| Shapiro and Bassen | 77 | 12 | 6.7 |

**Comment.** After reviewing the literature, we believe that our findings in the present study lend confirmation to some already established facts and also throw new light on the hematologic picture of the neonatal period.

*White Blood Cells.* It is reasonable to regard the leukocyte picture at birth as a reflection of hemopoietic hyperactivity during fetal existence. Evidence of this is the high cell count and presence in the blood of immature myeloid cells. It has been assumed that the drop in the white cell count and disappearance of the immature myeloid cells at the end of the first week are peripheral manifestations of decreased *production* of granulocytic leukocytes.[7] Our bone marrow findings offer another possible explanation for the change which takes place in the white cells. Although the blood differential reveals a shift to lymphocytic predominance at the end of the week, the absolute number of lymphocytes is but slightly higher than in the 1st day of life, whereas the myeloid elements show a marked relative and absolute decrease, with a shift to the right taking place. Since the myeloid cells, especially the younger forms, have actually increased in the bone marrow, it is suggested that during the 1st week of life there is a decreased *release* of the neutrophilic cells into the blood stream.

*Red Blood Cells.* The high red cell and hemoglobin content of the blood in the 1st day of life is a carry-over from fetal existence,

where low oxygen tension made necessary an abundance of oxygen-bearing cells. Stimulation of hemopoiesis toward this end is seen in the high percentage of nucleated red cells in the sternal marrow and in the peripheral blood findings of normoblasts and an elevated reticulocyte percentage.

At birth, the human organism is cast into a new environment, with the onset of respiration making necessary certain important physiologic changes. Basic needs must be met in a different manner, and the hemopoietic system adjusts itself accordingly.

As the result of some unknown mechanism *the formation of red cells is curtailed*. This is seen by the sharp drop of erythroid elements in the bone marrow and by the decrease of reticulocytes in the peripheral blood.

Many investigators agree with us that some drop in red blood cells and hemoglobin begins during the 1st week of life. On the other hand, the bone marrow findings of decreased red cell production do not necessarily contradict the reports of others[13,22,24,32,42,48,66,76] who have found a fall in red blood cells and hemoglobin taking place only after the 1st or 2d week; for it is known that changes in the bone marrow may precede peripheral blood changes by a variable length of time. The drop in the reticulocyte percentage during the 1st week is apparently a peripheral reflection of the decreased erythroblastic activity noted in the bone marrow.

The idea of curtailment of red cell formation during the neonatal period is not an original one. Mackay[49b] suggested it, Josephs[39a,b] discussed it, and Faxen[24] emphasized it.

In 1936 Josephs[39b] wrote, "One may regard the processes which regulate the level of hemoglobin and red cells as tending to a state of equilibrium which is . . . . adjusted . . . . at a level . . . . that is 'normal' for a given set of conditions. . . . . The infant is born with a level of hemoglobin . . . . above that which is normal for extra-uterine life. As a result, all signs of regeneration quickly disappear and the hemoglobin falls. . . . ." Our point of view is completely in accord with that of Faxen, who said, "To understand all changes in the red blood picture it is important to bear in mind that the percentage of morphological elements and hemoglobin depends on two factors, new formation and destruction. . . . . It appears as if the function of the bone marrow . . . . has been pushed too much into the background. . . . . The rapid fall in the reticulocyte values in the first week of life, found by all investigators, indicates that a reduced new formation of blood cells plays an important part in the change occurring in the blood during the first week."

Heretofore, the neonatal fall in red cells and hemoglobin has generally been attributed to excessive peripheral destruction of the superabundant red cells carried over from fetal life. Evidence in favor of this is by no means universally accepted. On the other

hand, the bone marrow and reticulocyte changes offer clear-cut evidence of diminished red cell formation.

The question arises whether both processes occur at the same time. Although it is possible that following birth some increased peripheral destruction of red cells may take place, the bone marrow evidence of decreasing erythropoietic activity in the 1st week of life could, by itself alone, account for the changes which take place in the red blood cells during this period. These findings suggest that the red cell level falls because of decreased production while the rate of destruction remains constant.

The fact that formation of new red cells by the bone marrow is curtailed may explain why, after birth, there is an increasing deposition of iron in the infant liver.[1,61] This latter finding has been held as proof of accelerated blood destruction. In contradiction to this idea, however, it is evident that if the bone marrow has cut down on red cell production, it has no great need of the iron derived from red cells which continue to break down.

**Conclusions.** Peripheral blood studies and sternal puncture examinations were made on 35 normal full-term infants in the 1st 24 hours of life and again 1 week later.

In the peripheral blood our findings agreed with those of many other investigators. We noted initial high levels of RBC, Hb, WBC, and reticulocytes. There was a moderate decrease in RBC and Hb, a sharp fall in WBC and reticulocytes, and a change in the differential from myeloid to lymphocytic predominance at the end of the week.

The most striking finding in the bone marrow was a marked drop in the erythroid elements at the end of the 1st week of life. This finding, reflected in the peripheral blood by the decreasing reticulocytes, is evidence of curtailed production of new red cells. Consequently, we offer the idea that the fall in RBC and Hb which takes place after birth is primarily the result of physiologic disintegration of the superabundant red cells carried over from fetal life, in the presence of diminished erythropoiesis.

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# EFFECT OF TOPICAL APPLICATION OF 2-METHYL-1,4-NAPHTHOQUINONE (SYNTHETIC VITAMIN K ANALOGUE) ON THE PROTHROMBIN LEVEL OF NEWBORN INFANTS.

## WITH REFERENCE TO A SIMPLIFIED MICRO-PROTHROMBIN TEST.

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Hemorrhagic disease of the newborn is now known to be a type of vitamin K deficiency caused by a hypoprothrombinemia which occurs during the first few days of life.[1,8,14,16] In most newborns physiologic hypoprothrombinemia lasts only a few days and the prothrombin level reaches normal in 6 to 10 days, probably because of the establishment of a bacterial flora in the intestinal tract following the ingestion of food.[13a,b,14]

The physiologic hypoprothrombinemia of the newborn may be prevented by giving vitamin K orally soon after birth.[2,5,12,16] The prothrombin level of the newborn may also be increased by giving vitamin K to the mother previous to delivery.[6,9,15,17] There are obvious disadvantages to both of these methods, such as intolerance to the vitamin or its analogue when given orally or when the onset of labor before the calculated date prevents the timely administration of vitamin K prepartum.

Since vitamin K belongs to the group of fat soluble vitamins (A, D, E and K) it is not unreasonable to suspect that it might be absorbed through the skin. de Beer *et al.*[3] have shown that 2-methyl-1,4-naphthoquinone in suitable vehicles administered percutaneously to vitamin K deficient chicks will effect a cure. A single dose of 1γ per chick cured 50% of the depleted chicks and larger doses afforded protection for relatively long periods of time.

Because of this report it seemed advisable to study the prothrombin levels of the blood of newborns following application of 2-methyl-1,4-naphthoquinone to the skin. A preparation of 2-methyl-1,4-naphthoquinone 1% in a specially prepared base* was used.

**Determination of Blood Prothrombin.** The difficulty of obtaining sufficient venous blood from newborns in order to obtain plasma for the determination of prothrombin level makes it necessary to use a micro-prothrombin test that employs capillary blood. Several such tests have been described. Quick[13c] reported a test using 1

* Supplied by Burroughs Wellcome & Co. (U. S. A.), Inc., New York.

drop each of whole blood and thromboplastin. A modification of Quick's original test has been reported by Kato[7] who used whole oxalated capillary blood to which is added the thromboplastin and calcium chloride solution. White *et al.*[18] reported on a method in which 10 c.mm. of thromboplastin and calcium chloride solution are placed side by side in a hanging drop slide and 10 c.mm. of blood obtained by puncture is added and mixed. A simple method described by Lawson,[10] employs a specially prepared thromboplastin solution. The blood obtained by puncture is added directly to the thromboplastin solution in the well of a hollow-ground slide.

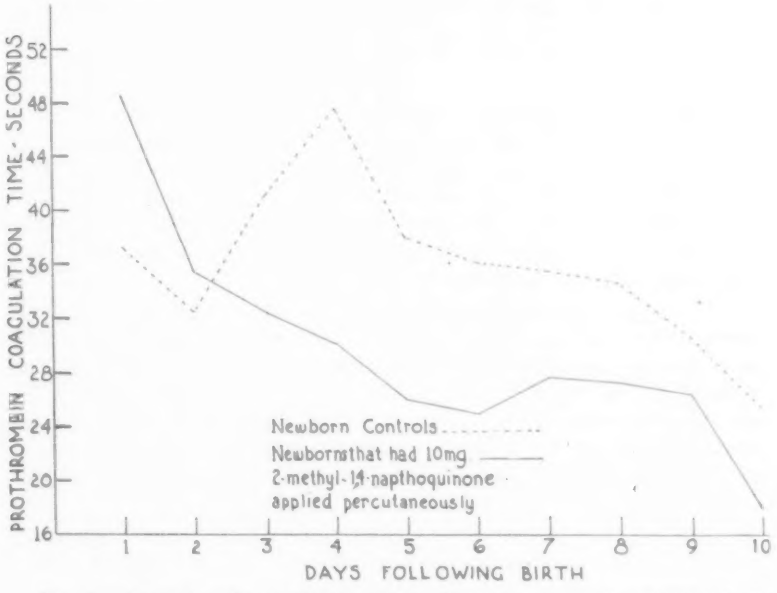


FIG. 1.—Average prothrombin coagulation time of a group of newborn infants and of a similar group that had 10 mg. 2-methyl-1,4-napthoquinone applied percutaneously during the first 48 hours following birth.

**Simplified Method of Micro-prothrombin Determination.** Previously we reported[11] on a simplified method of determining the prothrombin level in oxalated plasma by substituting Russell viper venom for the thromboplastin solution obtained from rabbit brain such as is used in Quick's method.

This method has been adapted for use with small amounts of capillary blood and has been satisfactory for use in determining prothrombin levels in newborn infants.

The test can best be performed in the nursery at the newborn's bedside. The newborn's heel or toe is cleaned with alcohol and a deep puncture is made with a lancet or needle so that the blood flows freely. Twenty cubic millimeters of blood is drawn into a hemoglobin pipette and immediately placed in the well of a hollow-

ground slide that contains 0.0274 mg. potassium oxalate.* (The slides are previously prepared by placing in the well of each slide the solution of potassium oxalate and allowing it to dry.)

The blood is thoroughly mixed with the oxalate and to it is added 20 c.mm. of a 1 to 10,000 dilution of Russell viper venom† and 20 c.mm. of 1.11% calcium chloride solution. The slide is tilted from side to side and the end-point is taken at the moment that fibrin clots can be seen. The end-point is usually sharp and the prothrombin time is considered to be the number of seconds from the addition of the calcium chloride solution to the formation of fibrin clots. We consider the normal prothrombin coagulation time, by this method, to be 28 seconds or less.

The above test was performed on 48 newborn infants divided into two equal groups. One group served as control and the other group received one application of 10 mg. 2-methyl-1,4-naphthoquinone in an ointment base applied topically to the back. Usually the vitamin K ointment was applied during the first or second day following birth. Micro-prothrombin estimations were performed 3 times a week on each newborn infant during its period of hospitalization. Each newborn had 4 or 5 prothrombin estimations during the period of observation.

**Results.** The typical physiologic hypoprothrombinemia of the newborn was exhibited in 18 of the 24 newborns in the control group (Table 1). The highest prothrombin coagulation time was present on the 4th day of life and decreased to the normal level at the 8th to 10th day with the exception of Case 21 which was 40 seconds on the 10th day.

The group that had 10 mg. 2-methyl-1,4-naphthoquinone applied to the skin of the back on the 1st or 2d day of life did not show any increase in prothrombin coagulation time (Table 2). The prothrombin coagulation time showed a steady decrease and was within normal limits by the 5th day. No newborn treated in this manner exhibited the so-called physiologic hypoprothrombinemia.

In order to determine if the average prothrombin coagulation observed for the two groups on the 4th day were significantly different, the "t" value was obtained and found to be 7.6‡ which

* Potassium oxalate solution was prepared by diluting 1 cc. 20% solution potassium oxalate to 450 cc. with distilled water. This represents approximately 0.0274 mg. per minim, and was found to be sufficient to prevent coagulation of the whole blood.

† Russell Viper Venom ("Stypven") supplied by Burroughs Wellcome & Co. (U. S. A.), Inc., New York.

‡ $$t = \frac{\bar{X}c - \bar{X}t}{S\sqrt{\frac{1}{Nc} + \frac{1}{Nt}}} = \frac{47.38 - 29.96}{11.03\sqrt{\frac{1}{12} + \frac{1}{8}}} = 7.6$$

$\bar{X}c$ = Average prothrombin coagulation time of control newborns.
$\bar{X}t$ = Average prothrombin coagulation time of treated newborns.
$S$ = Sum of squares of deviations from respective means.
$Nc$ = Number of cases in control group.
$Nt$ = Number of cases in treated group.

corresponds to probability greater than 0.001 according to the tables of Fisher and Yates.[4] It follows that when the difference between the two means is 7.6 times as great as the standard error, the difference observed between the treated and the control newborns is not accidental but is the result of some definite cause, being, in this study, the percutaneous administration of 2-methyl-1,-4-naphthoquinone ointment.

TABLE 1.—PROTHROMBIN COAGULATION TIMES OF NEWBORN CONTROLS.

| Days after birth: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Prothrombin time: | Sec. | Sec. | Sec. | Sec. | Sec. | Sec. | Sec. | Sec. | Sec. | Sec. |
| Case No. | | | | | | | | | | |
| 1 | .. | 31.0 | .. | .. | 51.1 | .. | 53.0 | .. | 29.5 | .. |
| 2 | 35.0 | .. | 34.0 | .. | 54.4 | .. | 32.2 | .. | 36.0 | .. |
| 3 | .. | 31.3 | .. | .. | 38.6 | .. | 29.0 | .. | 32.4 | .. |
| 4 | 26.8 | .. | .. | 75.8 | .. | 42.0 | .. | 33.5 | .. | .. |
| 5 | 19.1 | .. | .. | 55.0 | .. | 41.5 | .. | 32.8 | .. | .. |
| 6 | 31.8 | .. | 44.4 | .. | 21.5 | .. | .. | 28.6 | .. | 26.0 |
| 7 | .. | 30.8 | .. | 59.0 | .. | 25.3 | .. | .. | 31.6 | .. |
| 8 | .. | 32.5 | .. | 41.6 | .. | 34.0 | .. | .. | 30.0 | .. |
| 9 | 22.8 | .. | .. | 33.2 | .. | 39.8 | .. | 22.1 | .. | .. |
| 10 | .. | .. | 32.0 | .. | .. | 28.0 | .. | 39.1 | .. | 20.3 |
| 11 | .. | 46.0 | .. | 36.0 | .. | 29.7 | .. | .. | 30.4 | .. |
| 12 | 33.0 | .. | 65.7 | .. | .. | 36.4 | .. | 26.5 | .. | 22.7 |
| 13 | 49.7 | .. | .. | 34.7 | .. | 36.0 | .. | 25.0 | .. | .. |
| 14 | .. | 39.2 | .. | 41.8 | .. | 23.8 | .. | .. | 30.6 | .. |
| 15 | 30.0 | .. | 27.0 | .. | .. | 37.4 | .. | 25.6 | .. | 18.0 |
| 16 | 30.0 | .. | 43.5 | .. | .. | 57.0 | .. | 36.5 | .. | 25.6 |
| 17 | 52.0 | .. | .. | 55.5 | .. | 40.0 | .. | 42.6 | .. | .. |
| 18 | 34.2 | .. | 36.4 | .. | 34.6 | .. | 42.0 | .. | .. | .. |
| 19 | .. | 30.2 | .. | .. | 34.0 | .. | 36.5 | .. | 29.0 | .. |
| 20 | 50.0 | .. | .. | 31.0 | .. | 33.2 | .. | 59.0 | .. | .. |
| 21 | 47.0 | .. | 43.4 | .. | 35.4 | .. | .. | 45.0 | .. | 40.0 |
| 22 | .. | 24.0 | .. | 45.0 | .. | .. | 32.7 | .. | 24.0 | .. |
| 23 | .. | 26.5 | .. | 60.0 | .. | .. | 22.6 | .. | 29.0 | .. |
| 24 | 58.6 | .. | 43.5 | .. | 32.7 | .. | .. | 32.0 | .. | .. |
| Average | 37.1 | 32.4 | 41.1 | 47.4 | 37.8 | 36.0 | 35.4 | 34.5 | 30.3 | 25.4 |

TABLE 2.—PROTHROMBIN COAGULATION TIMES OF NEWBORNS THAT RECEIVED 10 MG. 2-METHYL-1,4-NAPHTHOQUINONE PERCUTANEOUSLY.

| Days after birth: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Prothrombin time: | Sec. | Sec. | Sec. | Sec. | Sec. | Sec. | Sec. | Sec. | Sec. | Sec. |
| Case No. | | | | | | | | | | |
| 1 | 30.8 | .. | .. | 29.8 | .. | 21.4 | .. | 29.0 | .. | .. |
| 2 | .. | 34.0 | .. | 30.0 | .. | 28.9 | .. | .. | .. | .. |
| 3 | 50.4 | .. | 30.1 | .. | 22.6 | .. | .. | 26.4 | .. | .. |
| 4 | 53.0 | .. | 33.7 | .. | 25.2 | .. | 32.6 | .. | .. | .. |
| 5 | 34.4 | .. | 23.3 | .. | 18.2 | .. | 24.0 | .. | .. | .. |
| 6 | .. | 31.2 | .. | 27.0 | .. | 22.1 | .. | .. | 31.2 | .. |
| 7 | 38.7 | .. | 33.4 | .. | 29.0 | .. | .. | 28.9 | .. | .. |
| 8 | .. | 37.0 | .. | 33.0 | .. | 27.5 | .. | .. | 29.6 | .. |
| 9 | 36.2 | .. | 36.0 | .. | 23.6 | .. | .. | 26.5 | .. | .. |
| 10 | 57.7 | .. | .. | 38.2 | .. | 23.1 | .. | 22.5 | .. | .. |
| 11 | 47.0 | .. | 26.1 | .. | .. | 27.6 | .. | 30.0 | .. | .. |
| 12 | 57.0 | .. | 51.6 | .. | .. | .. | 41.0 | .. | 26.8 | .. |
| 13 | 41.1 | .. | 29.5 | .. | .. | 28.5 | .. | 24.0 | .. | .. |
| 14 | 42.0 | .. | 32.0 | .. | 29.3 | .. | .. | 28.4 | .. | .. |
| 15 | 40.0 | .. | 33.0 | .. | .. | 28.2 | .. | 27.0 | .. | .. |
| 16 | 50.0 | .. | .. | 30.5 | .. | 21.5 | .. | 30.1 | .. | .. |
| 17 | .. | 60.1 | .. | .. | 32.0 | .. | 27.5 | .. | 26.2 | .. |
| 18 | .. | 32.4 | .. | 28.2 | .. | .. | 22.0 | .. | 19.0 | .. |
| 19 | 97.0 | .. | 38.4 | .. | 35.0 | .. | .. | 44.5 | .. | 18.0 |
| 20 | 47.6 | .. | 27.3 | .. | 25.0 | .. | .. | 28.0 | .. | .. |
| 21 | 92.0 | .. | 42.2 | .. | 21.6 | .. | .. | 24.4 | .. | .. |
| 22 | 26.0 | .. | 25.1 | .. | 21.0 | .. | 23.0 | .. | .. | .. |
| 23 | 47.0 | 18.0 | .. | 23.0 | .. | 19.2 | .. | 20.1 | .. | .. |
| 24 | 31.0 | .. | 26.2 | .. | 26.0 | .. | 24.0 | .. | .. | .. |
| Average | 48.3 | 35.5 | 32.5 | 30.0 | 25.7 | 24.8 | 27.7 | 27.2 | 26.6 | 18.0 |

No untoward effects from the 2-methyl-1,4-naphthoquinone ointment were observed in any newborn.

**Summary and Conclusions.** A simplified micro-prothrombin test has been described which has obvious advantages over methods that employ unstable thromboplastic substances. The Russell viper

venom used as the thromboplastic agent is stable for several weeks when kept in a refrigerator and does not require time-consuming laboratory preparation. We believe that this simplified test which requires no special apparatus or unstable reagents can be performed by the practitioner at the bedside.

Data have been presented in this study showing that the percutaneous application of 2-methyl-1,4-naphthoquinone (Synthetic Vitamin K analogue) in an ointment base will prevent hypoprothrombinemia of the newborn. As this method is simple and effective it is suggested that it be used routinely as a prophylactic measure in preventing hypoprothrombinemia of the newborn. As a routine procedure 10 mg. of 2-methyl-1,4-naphthoquinone in a special ointment can be rubbed thoroughly on the skin of the back during the 1st or 2d day of life. As a single application was effective in our series we do not believe that the application need be repeated.

We wish to thank Dr. E. J. de Beer of the Experimental Research Laboratories of Burroughs Wellcome & Co. for his assistance and advice in preparing the statistical analysis of the data obtained in this experiment.

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## THE EFFECTIVENESS OF PRENATAL ADMINISTRATION OF 2 METHYL 1, 4 NAPHTHOQUINONE IN MAINTAINING NORMAL PROTHROMBIN LEVELS IN INFANTS.*

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Two factors have contributed to more complete understanding and effective treatment of hemorrhagic diseases in infants: the

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introduction of accurate micro methods of determining the prothrombin level of the blood, and the discovery that vitamin K is a potent factor in maintaining a normal prothrombin level. This led in turn to the discovery that the prothrombin time tends to be greatly prolonged in infants showing hemorrhagic manifestations, in which case the administration of vitamin K to such infants results in rapid improvement and establishment of a normal prothrombin level.

In spite of considerable variation in methods and results, a number of facts have been established. First, in newborn infants the prothrombin level during the first 24 hours appears to be within normal limits or slightly under normal, with a fall to a definitely low level between the second and the fourth days.[1,2,4,7–10,12,14,19a] A gradual return to normal or almost so occurs at the end of a week or 10 days. Although the prothrombin may fall to a very low level, hemorrhagic manifestations do not necessarily occur.[9] Furthermore, direct treatment of newborn infants with vitamin K by mouth results in a prompt increase of the prothrombin to normal, or if given early enough, in prevention of the usual drop of the prothrombin level.[4,8–10,12,13,17,19a]

Evidence has been presented[3–5,10,11,17,18,19b,20] that treatment of the mother with vitamin K helps in maintaining a normal prothrombin level in the infant. The results, however, are not entirely conclusive since in most instances prothrombin was determined on the first day of life only. Since relatively high prothrombin levels existing on the first day of life are followed by a distinct drop, usually on the second day, the results cannot be properly evaluated unless observations are continued through this more critical period. A number of the reports cited deal with small numbers of subjects.

The investigation reported here was undertaken in order to determine the efficiency of 2-methyl-1, 4-naphthoquinone, one of the synthetic forms of vitamin K, in maintaining normal prothrombin levels in newborn infants when given to the mothers during the last weeks of pregnancy. A second objective was to ascertain the extent of the need for vitamin K therapy during pregnancy in the population served by this institution: the unemployed, laboring, and lower middle classes of the eastern industrial region.

**Methods and Materials.** Prothrombin was determined in plasma of 25 infants whose mothers had received tablets* containing 2 mg. of 2-methyl-1, 4-naphthoquinone together with 0.2 gm. of purified bile salts daily by mouth for varying periods of time during the last month of pregnancy. Twenty-five infants whose mothers received no treatment were used as controls. Plasma prothrombin of the infants was determined on the first day, between the second and fourth day, and again on the sixth or seventh day after delivery. Cases were chosen at random from patients registered in the prenatal clinic during October, November, December, and January. No untoward reactions were observed in the treated patients.

* Supplied by Jovan Laboratories, Inc.

Because of the technical difficulties of obtaining venous blood from newborn infants, the micro method devised by Hoffman and Custer[6] was used as follows: 5 c.mm. of blood obtained from the finger or heel was immediately transferred by means of a Custer hemoglobin pipette to a glass culture slide containing 5 c.mm. of a saline suspension of thromboplastin maintained at 37° C. on a hot plate. The mixture was then gently and slowly stirred with a platinum wire, and the time necessary for coagulation ascertained by means of a stop watch. All determinations were made in duplicate and the average taken. The variation was small. A fresh puncture was made for each determination, a spring lancet being used to insure a free flow of blood. A control was run in every case, using in most instances the same normal individual. The thromboplastin was prepared by Quick's[15c] method.

Control determinations by this method showed the average prothrombin time to be 12.7 seconds. These figures are based on 48 different determinations made on 4 normal individuals. Results of determinations on normal subjects by Quick's method showed close agreement with those of the Hoffman-Custer method. In order to correct for the varying potency of the thromboplastin (thromboplastin emulsion was prepared freshly each day), the following formula[16] was used:

$$\frac{\text{prothrombin time of infant} \times 12.5}{\text{prothrombin time of control}} = \text{corrected prothrombin time.}$$

The corrected prothrombin time was then converted to prothrombin percentage of normal by means of the graph published by Quick.[15b]

TABLE 1.—THE PLASMA PROTHROMBIN OF 25 UNTREATED CASES.

| | Prothrombin, % of normal. | | | |
|---|---|---|---|---|
| | | Infant. | | |
| Case No. | Mother. | 1st day. | 2d–4th day. | 6th–7th day. |
| 1 | 60 | .. | 70 | 100 |
| 2 | 85 | .. | 9 | 60 |
| 3 | 100 | 30 | 30 | 45 |
| 4 | 95 | .. | 40/35 | 100 |
| 5 | 95 | 100 | 40 | .. |
| 6 | 98 | .. | 25 | 100 |
| 7 | 55 | 16 | 8 | 80 |
| 8 | 100 | .. | 40 | .. |
| 9 | 65 | 45 | 33 | 85 |
| 10 | 100 | 100 | 37 | .. |
| 11 | 100 | 100 | 69 | 100 |
| 12 | 100 | 45 | 43 | 33 |
| 13 | 65 | 37 | 8 | .. |
| 14 | 100 | 90 | 65 | 100 |
| 15 | 100 | 67 | 70 | 85 |
| 16 | 75 | 100 | 60 | .. |
| 17 | 100 | 100 | 100 | .. |
| 18 | 100 | 85 | 40 | 100 |
| 19 | 90 | 70 | 38* | 60* |
| 20 | 70 | 90 | 33 | 100 |
| 21 | 80 | 67 | 40 | 100 |
| 22 | 100 | 90 | 33 | 37 |
| 23 | 65 | 53 | 45 | 63 |
| 24 | 100 | 95 | 37 | 40 |
| 25 | 75 | 70 | 60 | .. |
| Average | 88 | 72 | 43 | 77 |

* Vaginal bleeding, 3d to 8th day.

**Results.** Tables 1 and 2 show the plasma prothrombin levels expressed as per cent of normal of 50 untreated pregnant women, 25 in the control group and 25 in the treated group. The average value of 89 per cent for this entire group may be taken as a normal standard for this study. It may be seen in Table 2 that there is no significant difference in the average prothrombin level of the mothers before and after receiving treatment with 2-methyl-1, 4-naphthoquinone.

On the first day of life, infants of untreated mothers (Table 1) show an average prothrombin of 72%, as compared with an average value of 86% for infants whose mothers received treatment with vitamin K (Table 2). This difference is not significant.*

TABLE 2.—THE PLASMA PROTHROMBIN OF 25 TREATED CASES.

| | | Prothrombin, % of normal. | | | | |
|---|---|---|---|---|---|---|
| | | Mother. | | Infant. | | |
| Case No. | Duration of treatment (days). | Before treatment. | After treatment. | 1st day. | 2d–4th day. | 6th–7th day. |
| 1† | 20 | 100 | 100 | (40) | (48) | .. |
| 2 | 7 | 80 | 95 | 82 | 100 | 100 |
| 3 | 21 | 80 | 100 | 80 | 70 | .. |
| 4 | 12 | 90 | 90 | 80 | 90 | 100 |
| 5 | 6 | 80 | 90 | 100 | 85 | 100 |
| 6 | 17 | 100 | 100 | 35 | 58 | 100 |
| 7 | 25 | 100 | 60 | .. | 85 | 85 |
| 8 | ? | 50 | 75 | .. | 78 | 85 |
| 9 | 21 | 100 | 99 | 100 | 50 | 45 |
| 10 | 11 | 100 | 100 | 60 | 100 | .. |
| 11 | 28 | 98 | 100 | 90 | 100 | 100 |
| 12 | 17 | 100 | 70 | 75 | 83 | .. |
| 13 | 9 | 98 | 100 | 99 | 100 | 100 |
| 14 | 20 | 100 | 75 | .. | 70 | 100 |
| 15 | 12 | 70 | 100 | 100 | 90 | 100 |
| 16 | 10 | 100 | 100 | 100 | 100 | 90 |
| 17 | 9 | 90 | 100 | 100 | 100 | 85 |
| 18 | 20 | 100 | 100 | 100 | 100 | .. |
| 19 | 10 | 85 | 85 | 85 | 100 | 100 |
| 20 | 5 | 100 | 100 | 100 | 85 | .. |
| 21 | 24 | 100 | 100 | 85 | 70 | 70 |
| 22* | 24‡ | 100 | 100 | (85) | (45) | (55) |
| 23 | 10 | 90 | 85 | .. | 100 | 100 |
| 24 | 9 | 65 | 95 | 70 | 85 | .. |
| 25 | 15 | 70 | 80 | .. | 80 | 90 |
| Average | | 90 | 92 | 86 | 86 | 89 |

During the second to fourth day period the infants whose mothers had received no treatment showed a distinct drop of the prothrombin level to an average value of 43% (Table 1). The corresponding value for infants of treated mothers was 86% (Table 2). This difference is highly significant.* Individual values in the untreated

* Tested by Student's method for determining "t".
† Omitted from calculation of mean.
‡ No medication for 2 weeks prior to delivery.

group ranged from 8 to 100%, with only 4 cases having prothrombin levels above 65%. In the treated group, prothrombin ranged from 50 to 100% with only 4 patients showing less than 70%.

By the sixth to seventh day, the average prothrombin level had increased to 77% in the untreated cases, and 89% in the treated cases. Although this difference is not significant,* 7 of 18 determinations made at this time on untreated infants gave results below normal and in 4 the deficiency was marked. In the treated group only 2 cases fell below 70%.

Of the 4 infants in the treated group that showed abnormally low prothrombin levels, the mother of one (Case 1) was thought to have been uncoöperative in taking the medication, while another (Case 22) finished her supply 2 weeks before delivery and did not return for more. Consequently both were omitted in calculating the average values. No reason for failure could be found in Cases 6 and 9.

**Discussion.** Infants from untreated mothers having normal prothrombin levels usually exhibit a normal level during the first day of life. The prothrombin rapidly falls to an abnormally low level after the first day, but by the end of the first week has in most cases again risen to normal. This drop varies in degree. A low prothrombin level alone does not seem to be sufficient to induce spontaneous hemorrhage, since only one baby of those with dangerously low prothrombin showed such a tendency.

Prothrombin remained normal with few exceptions in those infants whose mothers received vitamin K during the last weeks of pregnancy, if only for so short a period as 5 days. In 2 of 4 infants failing to show a response to prenatal therapy there were circumstances indicating that the failure was not due to the ineffectiveness of the drug.

These results are compatible with the assumption that the newborn infant is endowed with sufficient prothrombin to last for approximately 24 hours, and is then faced with an interval when, due to lack of an adequate supply of vitamin K, this inherited prothrombin is used up without sufficient new being formed. Soon after the infant begins to take and absorb nourishment a normal level is built up by the liver, although in most cases a week is required before normal levels are established. It seems probable that in infants whose mothers have received vitamin K therapy a sufficient amount of this substance is carried over in the fetal blood supply to tide the infant over the danger period and allow the earlier production of prothrombin by its own liver.

The effectiveness of 2-methyl-1, 4-naphthoquinone administered prenatally for maintenance of normal prothrombin in the newborn is demonstrated by this study.

**Summary.** 1. About $\frac{3}{4}$ of the infants of untreated mothers exhibited a significant drop to an abnormally low average prothrombin level

* Tested by Student's method for determining "t".

within 48 to 96 hours after birth, with a rise to a normal level by the end of the first week.

2. Infants whose mothers had received 2-methyl-1, 4-naphthoquinone from 5 to 28 days prior to delivery were protected against the fall in prothrombin in all but 2 of 23 cases.

3. Occasional subnormal prothrombin levels were observed in a group of 50 pregnant women examined shortly before term.

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## PERIPHERAL CIRCULATORY FAILURE IN DIABETIC ACIDOSIS AND ITS RELATION TO TREATMENT.*

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The presence of peripheral circulatory failure in diabetic acidosis has been recognized clinically for many years. Fagge,[7] in 1874, described a case of acidosis which improved after the intravenous administration of saline solution. Peters[15,16] has attributed to the

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shock syndrome certain chemical changes* in diabetic acidosis. In 1928, Allen[1] called attention to the clinical picture of "shock" in diabetic acidosis of long standing. Atchley,[2a] in 1930, used the term "medical shock" to describe the clinical picture of severe diabetic acidosis. In 1930, Lawrence,[13] and in 1934, Atchley[2] reemphasized the importance of treatment of "medical shock" in diseases, notably diabetic acidosis, associated with marked dehydration.

The clinical picture of patients who are moribund in uncomplicated diabetic acidosis is characterized by a rapid pulse of poor volume, a falling blood pressure, a rising body temperature, deepening unconsciousness ending in death. This sequence of events occurs despite treatment with insulin, glucose, alkalies and fluids. Death may occur while the blood sugar concentration and $CO_2$ combining power values are nearly normal. If the alterations in blood sugar concentration and $CO_2$ combining power represent the metabolic disturbances responsible for the condition of these patients, why should they die when the metabolic disturbances, as represented by these chemical data, are corrected?

Postmortem examination of patients dying in uncomplicated diabetic acidosis affords little help in establishing the mechanism of death. Warren's[18] description of the pathologic findings in cases of diabetic acidosis can be summarized by the following quotations: "The pathological changes in coma are conspicuous by their absence. Even in pre-insulin days when diabetic coma developed in uncomplicated cases of diabetes there were no characteristic pathological changes that would enable one at post mortem or on looking at a section of tissue to say 'This material came from a case of diabetic coma.' Today the same holds true." The only constant finding was evidence of gastro-intestinal hemorrhage. Dillon, Riggs and Dyer[6] described brain lesions in "fatal diabetic acidosis like those seen in acute asphyxia. The primary pathologic changes occur in the cerebral capillary bed. The capillaries are dilated, and the endothelial cells show degenerative changes with increased permeability of the walls as evidenced by the presence of perivascular and pericellular edema. As a result of the cerebral edema there is proliferation of neuroglia, especially in the subependymal and marginal areas, and acute degenerative changes in the ganglion cells."

Since death frequently occurs in these patients whose diabetic chemically disordered function has been corrected by treatment, and postmortem examination of these patients yields little evidence in establishing a mechanism for death, it seemed reasonable to look for a disturbance of function which might be sufficient to cause death and yet not leave diagnostic postmortem changes. The clinical impression of Allen, Peters, Atchley and others of the existence of "medical shock" in diabetic acidosis and the clinical picture of peripheral circulatory failure which we have also observed

* Serum proteins, blood cell volume and oxygen capacity.

suggested the direction for the investigation of the disturbance of function.

**Methods.** The patients studied were selected from those admitted in diabetic acidosis to the Metabolic Division of the Philadelphia General Hospital, services of Dr. E. S. Dillon and Dr. A. J. Sindoni, Jr.

Temperature, pulse rate, blood pressure and respiratory rate were recorded every half hour. Blood sugar and $CO_2$ combining power determinations were made on admission and were repeated every 3 hours throughout the course of treatment until recovery or death had occurred. Blood sugar determinations were made by a modified method of Folin and Wu and $CO_2$ combining power of plasma was determined by the method of Van Slyke and Cullen.[14a]

Blood for examination was drawn without stasis from the femoral artery and vein in oiled syringes and placed in tubes containing potassium oxalate and paraffin oil. Arterial and venous oxygen content, $CO_2$ content, and oxygen capacity were determined by the method of Van Slyke and Neill.[14b] Serum proteins, hemoglobin and cell volume by hematocrit were measured. Kingsley's photoelectric biuret[12] method was used for serum protein, and the Sanford, Sheard and Osterberg photo-electric colorimetric method[17] was used for hemoglobin determinations. Packed cell volume measurements were made from Wintrobe hematocrit tubes after centrifuging for 30 minutes. These studies were repeated during the course of treatment and again after recovery.

Peripheral bloodflow in the hand was measured by the plethysmograph and was recorded soon after admission and as often as possible thereafter until recovery or death. Freeman's modification[5a] of the original method of Hewlett and Van Zwalwenburg was used.

**Results.** One group of patients with diabetic acidosis had a reduced peripheral circulation which, however, was compensated and recovered following treatment. These patients were conscious, had little or no reduction in blood pressure and had moderate reductions in peripheral bloodflow. Figure 1 shows the course of such a patient. This patient was admitted to the hospital in acidosis after a dietary indiscretion with a blood pressure of 130/70 mm. of mercury, a pulse rate of 116 per minute, and a reduced bloodflow (3.6 to 5.7 cc./100 cc. of hand per minute). The venous oxygen saturation was 88.8% on admission but during treatment fell to 59.5%; after recovery it was 86%. The patient absorbed fluids given by hypodermoclysis and showed an increased bloodflow before intravenous fluids were given. Treatment was accompanied by an increase in peripheral bloodflow and a decrease in venous oxygen saturation.

A second group had diabetic acidosis with peripheral circulatory failure and recovered after treatment. They were semiconscious or unconscious, had marked reduction in blood pressure and peripheral bloodflow. The course of one is shown in Figure 2. This patient was a newly discovered diabetic in whom acidosis was probably precipitated by pharyngitis with cervical adenitis. On admission to the wards his blood pressure was 50/30 mm. of mercury, pulse rate 120 per minute, peripheral bloodflow was not recordable, and

venous oxygen saturation was 63.8%. Plasma and 6% acacia were given before bloodflow could be recorded. The bloodflow increase and the rise in blood pressure were maintained. The patient

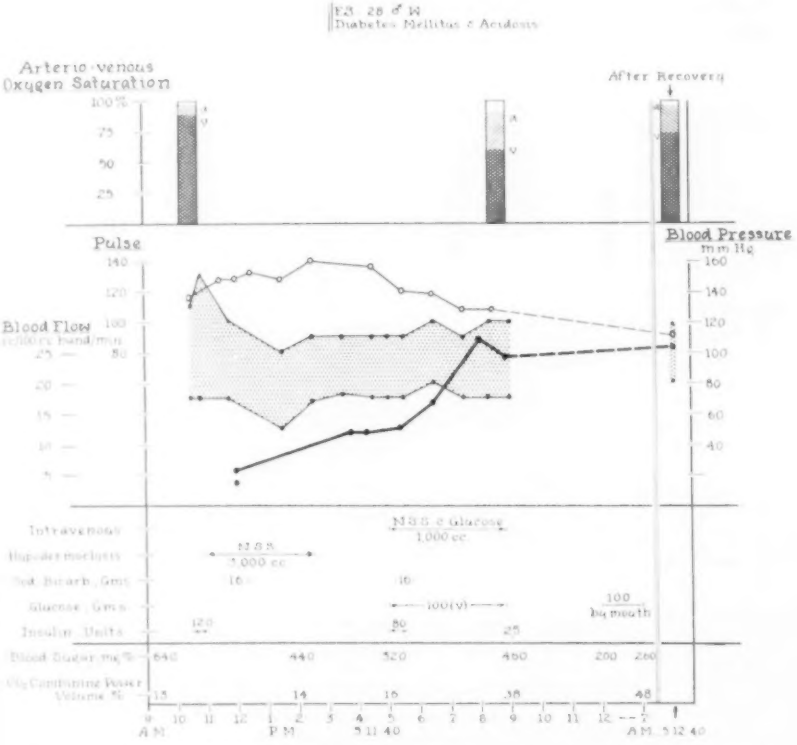


FIG. 1.—Diabetic Acidosis—Peripheral Circulation Compensated (Recovered): Course of Case 2.

*On admission:* The patient was conscious. He had a moderately reduced peripheral circulation but a maintained blood pressure. Venous oxygen saturation was 88.8%.

*During treatment:* Peripheral bloodflow increased and was maintained following the administration of saline solution by hypodermoclysis. The intravenous infusion was given to supply glucose rather than to increase circulation. Venous oxygen saturation decreased while peripheral bloodflow increased during treatment. The general condition of the patient was more closely correlated with the state of the circulation than with the level of the $CO_2$ combining power.

Abscissæ: Time in hours.

Ordinates: Blood sugar concentration and $CO_2$ combining power values. Treatment administered and time required for each item of treatment. Peripheral bloodflow, pulse rate, blood pressure and arterial and venous oxygen saturation.

became conscious soon after the rise in blood pressure and bloodflow. This took place 4 hours after treatment was started but long before the blood ketone body level fell. During treatment the venous oxygen saturation was 68%. After recovery the venous

oxygen saturation was 78% in the presence of a rapid bloodflow. The presence of a venous oxygen saturation of 63.8% with marked reduction of bloodflow in this patient, in contrast to the venous oxygen saturation of 88.8% with less marked reduction in bloodflow in the case shown in Figure 1, may be the result of a more advanced state of peripheral circulatory failure.

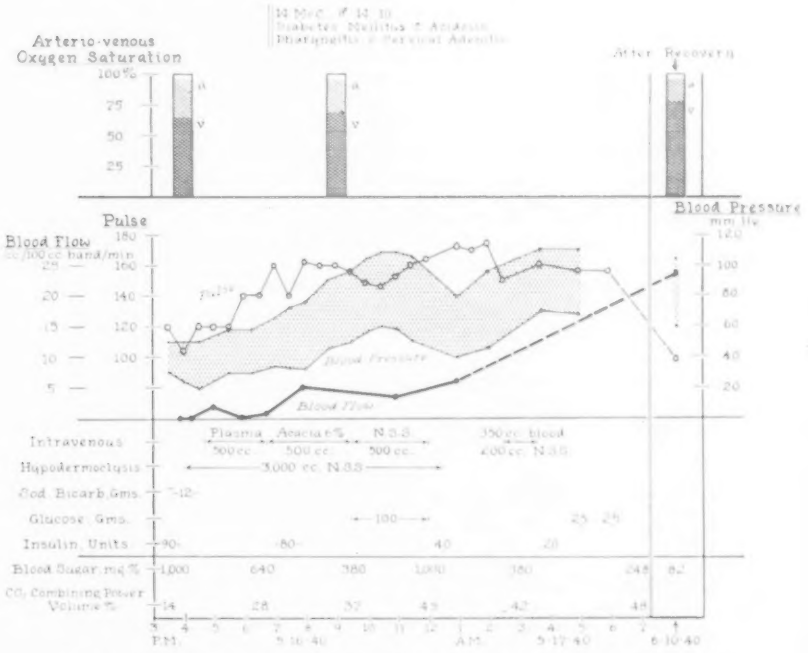


FIG. 2.—Diabetic Acidosis With Peripheral Circulatory Failure (Recovered): Course of Case 6.

*On admission:* The patient was unconscious, his extremities were cool and his skin was mottled. Blood pressure and peripheral bloodflow were markedly reduced. Venous oxygen saturation was 63.8% in the presence of a reduced circulation.

*During treatment:* Peripheral bloodflow and blood pressure were increased and maintained only after the administration of osmotically active fluids by the intravenous route. The patient regained consciousness at 7:30 P.M., coincident with an increase in peripheral bloodflow and blood pressure. Venous oxygen saturation was 68% in the presence of an increased circulation. The general condition of the patient was closely correlated with the state of the circulation.

Abscissæ and ordinates as in Figure 1.

A third group had diabetic acidosis with peripheral circulatory failure but died despite treatment. Figure 3 shows the course of one of these patients who had lost consciousness and showed marked reduction in blood pressure and bloodflow. This patient had a cellulitis of the neck which was probably responsible for the onset of acidosis. On admission to the wards, the blood pressure was 68/40 mm. of mercury, pulse rate 116 per minute, bloodflow 1.2 cc./100 cc. of hand per minute, and the venous oxygen saturation was

64.2%. Blood pressure and blood flow rose only after administration of 6% acacia intravenously. This increase was not maintained. Here again, the venous oxygen saturation of 64% contrasted to venous oxygen saturations of 83% to 88.8% in patients with the same degree of reduction of bloodflow may indicate a more severe failure of the peripheral circulation.

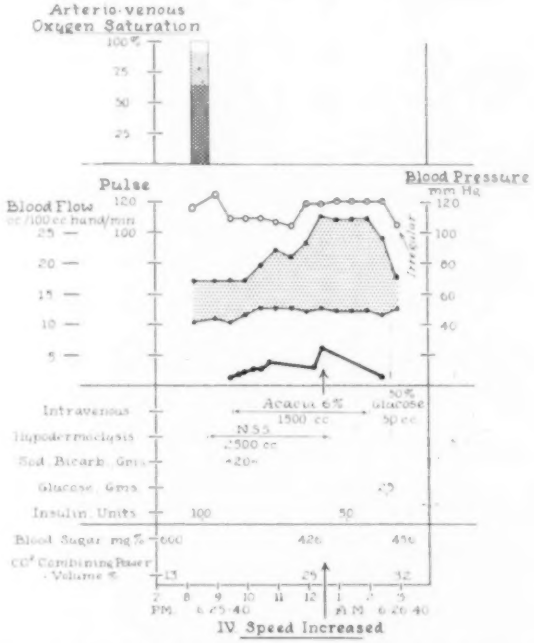


FIG. 3.—Diabetic Acidosis With Peripheral Circulatory Failure (Died): Course of Case 7.

*On admission:* The patient was unconscious. She had a marked reduction of peripheral bloodflow and blood pressure. Venous oxygen saturation was 64.2%.

*During treatment:* There was a failure to maintain an increased peripheral bloodflow and blood pressure despite the administration of osmotically active solutions by the intravenous route. The $CO_2$ combining power values rose during treatment. This case likewise illustrates the close correlation between the general condition of the patient and the state of the circulation.

Abscissæ and ordinates as in Figure 1.

The findings obtained in all of the patients studied are summarized in Table 1. Peripheral bloodflow was reduced in all patients on admission. The patients with the most marked reductions were most seriously ill, were unconscious and had lowest blood pressures. Bloodflow increased markedly during treatment. Sudden marked increases in flow were usually associated with increase in speed of intravenous infusion.

TABLE 1.—SUMMARY OF RESULTS.

| Patient. | Date, 1940. | Time. | Serum proteins, gm. per 100 cc. Arterial. | Serum proteins, gm. per 100 cc. Venous. | Hemoglobin, gm. per 100 cc. Arterial. | Hemoglobin, gm. per 100 cc. Venous. | Hematocrit, % c. Arterial. | Hematocrit, % c. Venous. | Blood sugar,* venous, mg. per 100 cc. | Blood $CO_2$ content, vol. % c. Arterial. | Blood $CO_2$ content, vol. % c. Venous. | Oxygen content, vol. % c. Arterial. | Oxygen content, vol. % c. Venous. | Oxygen capacity, vol. % c. Arterial. | Oxygen capacity, vol. % c. Venous. | Oxygen saturation, % c. Arterial. | Oxygen saturation, % c. Venous. | Blood pressure, mm. mercury. | Bloodflow, cc. blood per 100 cc. Hand per minute. | Oxygen utilization, cc. oxygen per 100 cc. Hand per min. | Mental state. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **GROUP I. PERIPHERAL CIRCULATION COMPENSATED. RECOVERED.** | | | | | | | | | | | | | | | | | | | | | |
| 1. J. McD. 31 M W | 4/6 | 12:00 N on adm. | 10.3 | 9.9 | 16.9 | 16.7 | 55.8 | 57.5 | 620 | 13.4 | 15.4 | 21.8 | 19.1 | 22.6 | 22.4 | 96.4 | 85.3 | 100/70 | 3.9 | 0.11 | Conscious |
| | 4/6 | 6:00 P.M. during treat. | 9.9 | 9.9 | 16.7 | 16.7 | 58.1 | 56.3 | 440 | 31.1 | 37.2 | 19.8 | 14.0 | 22.2 | 22.4 | 89.2 | 62.5 | 100/80 | 8.2 | 0.48 | Conscious |
| | 4/8 | 8:00 P.M. after recov. | 5.5 | 5.4 | 14.0 | 14.1 | 41.0 | 42.5 | 163 | 52.0 | 55.1 | 17.0 | 13.5 | 18.7 | 18.9 | 90.9 | 71.4 | .... | 5.5 | 0.25 | Conscious |
| 2. F. S. | 5/11 | 10:30 A.M. on adm. | 9.4 | 9.3 | 18.0 | .... | 50.0 | .... | 640 | 6.0 | 11.0 | 23.7 | 20.3 | .... | 24.2 | 97.8 | 88.8 | 120/70 | 3.7 | 0.12 | Conscious |
| 28 M W | 5/11 | 8:30 P.M. during treat. | 7.4 | 7.3 | 16.0 | 16.1 | 45.4 | 46.3 | 460 | 30.2 | 35.8 | 20.6 | 13.4 | 22.5 | .... | 91.5 | 59.5 | 120/70 | 27.1 | 1.95 | Conscious |
| | 5/12 | 11:45 A.M. after recov. | 7.2 | 7.3 | 15.0 | 15.1 | 41.0 | 41.6 | 260 | 40.6 | 44.3 | 19.7 | 17.4 | 20.3 | .... | 97.0 | 85.6 | 118/80 | 22.6 | 0.52 | Conscious |
| **GROUP II. PERIPHERAL CIRCULATORY FAILURE. RECOVERED.** | | | | | | | | | | | | | | | | | | | | | |
| 3. R. C. 36 M B | 5/30 | 10:45 P.M. on adm. | 8.1 | 8.0 | 16.1 | 16.2 | .... | 34.4 | 616 | 5.8 | 7.5 | 20.7 | 18.3 | .... | 21.5 | 96.3 | 85.1 | 88/52 | 1.0 | 0.02 | Semiconscious |
| | 5/31 | 4:15 A.M. during treat. | 7.6 | 7.6 | 14.8 | 14.9 | 28.2 | 31.5 | 330 | 19.1 | 24.2 | 19.5 | 14.2 | .... | 19.9 | 97.8 | 71.3 | 122/80 | 6.9 | 0.37 | Conscious |
| | 6/11 | 8:00 P.M. after recov. | 7.4 | ... | 13.2 | .... | 25.0 | .... | 118 | 34.6 | 42.8 | 16.8 | 9.5 | .... | 17.8 | 94.5 | 53.3 | 94/64 | 3.2 | 0.24 | Conscious |
| 4 H. H. 61 F W | 4/22 | 8:45 P.M. on adm. | 8.8 | 8.7 | 11.6 | 11.2 | 36.5 | 35.0 | 800 | 4.4 | 6.7 | 14.0 | 12.5 | 15.5 | 15.0 | 90.0 | 83.3 | | | | |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 H. H. 61 F W | 4/22 | 8:45 P.M. on adm. | 8.8 | 8.7 | 11.6 | 11.2 | 36.5 | 35.0 | 800 | 4.4 | 6.7<br>6.7† | 14.0 | 12.5<br>12.5† | 15.5 | 15.0 | 90.0 | 83.3 | 92/40 | 3.8 | 0.04 | Unconscious |
| | 4/23 | 3:30 A.M. during treat. | 5.8 | 5.4 | 9.5 | 9.2 | 21.7 | 21.3 | 400 | 24.2 | 25.0<br>25.8† | 10.8 | 9.1<br>9.3† | 12.7 | 12.3 | 84.7 | 73.8 | 120/60 | 32.8 | 0.56 | Semiconscious |
| | 4/23 | 3:30 P.M. during treat. | 4.8 | 4.5 | 10.5 | 10.5 | 29.3 | 26.2 | 370 | 43.0 | 46.8 | 13.0 | 11.3 | 14.1 | 14.1 | 92.3 | 80.3 | .... | 21.6 | 0.37 | Conscious |
| | 5/9 | 10:00 P.M. after recov. | 6.5 | 6.9 | 10.2 | 10.5 | 29.5 | 32.6 | 228 | 42.2 | 48.7<br>49.5† | 14.2 | 11.6<br>11.2† | .... | .... | .... | .... | 120/60 | 17.6 | 0.47 | Conscious |
| 5. R. W. 18 F W | 6/19 | 6:00 P.M. on adm. | 7.1 | 6.9 | .... | 9.5 | 17.9 | 21.9 | 600 | 6.4 | 8.6 | 12.0 | 10.7 | .... | 12.8 | 93.7 | 83.5 | 76/44 | 1.2 | 0.03 | Unconscious |
| | 6/19 | 10:30 P.M. during treat. | 5.0 | 4.7 | .... | 10.3 | 22.5 | 23.7 | 169 | 15.4 | 19.2 | 11.8 | 8.8 | .... | 12.5 | 94.3 | 70.4 | 118/88 | 3.4 | 0.10 | Conscious |
| | 7/8 | 9:30 P.M. after recov. | 6.8 | 6.2 | 11.9 | 11.8 | 24.6 | 26.9 | 320 | .... | .... | .... | .... | .... | .... | .... | .... | .... | 16.2 | .... | Conscious |
| | 7/12 | After recov. | .... | ... | .. . | .... | .... | .... | 236 | 47.0 | 51.0 | 13.7 | 11.8 | .... | 14.2 | 96.5 | 83.1 | 130/84 | 12.9 | 0.24 | Conscious |
| 6. W. McC. 10 M W | 5/16 | 4:00 P.M. on adm. | 7.9 | 7.8 | 14.7 | 14.6 | 41.5 | 42.8 | 1000 | 7.1 | 11.9 | 19.4 | 12.7 | .... | 19.9 | 97.5 | 63.8 | 50/30 | 0.0 | 0.0 | Unconscious |
| | 5/16 | 9:00 P.M. during treat. | 5.2 | 5.0 | 13.7 | 13.6 | .... | .... | 380 | 27.8 | 32.6 | 17.8 | 12.6 | .... | 18.5 | 96.3 | 68.0 | 76/34 | 7.0 | 0.36 | Semiconscious |
| | 6/10 | 9:30 P.M. after recov. | 6.3 | ... | .... | 10.8 | 35.3 | .... | 60 | 46.0 | 50.3 | 14.2 | 11.4 | 14.6 | .... | 97.3 | 78.0 | 104/60 | 23.6 | 0.66 | Conscious |
| | | | | | | | | | GROUP III. PERIPHERAL CIRCULATORY FAILURE. DIED. | | | | | | | | | | | | |
| 7. H. B. 65 F W | 6/25 | 8:30 P.M. on adm. | 6.7 | 6.8 | 16.6 | 14.8 | 33.8 | 32.3 | 600 | 6.3 | 12.0 | 17.9 | 12.2 | .... | 19.0 | 94.4 | 64.2 | 68/40 | 1.2 | 0.07 | Unconscious |
| 8. F. W.‡ 38 M B | 8/18 | 7:00 P.M. on adm. | 7.8 | 8.0 | 19.0 | .... | 33.0 | 34.0 | 640 | 8.8 | 11.4 | 23.9 | 11.4 | 25.1 | .... | 95.2 | 45.2 | 96/70<br>124/70 | ...<br>3.7 | ...<br>0.46 | Unconscious<br>Unconscious |

* Blood sugar determinations were not always made at the same time as the other studies. The values given are those obtained nearest the times listed.

† The blood drawn from superficial antecubital vein of arm in plethysmograph for comparison with femoral vein blood.

‡ Studies were made about 2 hours after insulin and fluids were given.

Determinations of oxygen content of arterial and venous blood showed a narrow difference between the 2 specimens. Venous oxygen saturation was high in the presence of reduced bloodflow. In 5 cases the arteriovenous oxygen difference was 1.3 to 3.4 vol. % and the venous oxygen saturation ranged from 83.3% to 88.8%. Cases 6 and 7 had arteriovenous differences of 5.1 and 6.7 vol. % of oxygen and venous oxygen saturation of 63.8% and 64.2%. Case 8 showed an arteriovenous difference of 12.6 vol. % oxygen and a venous oxygen saturation of 45.2%. This patient had received insulin and intravenous fluids at the time these studies were made. Venous oxygen saturation fell while blood flow rose during treatment in nearly all cases.

Estimations of oxygen utilization can be calculated from arteriovenous oxygen difference (1 cc. oxygen per 100 cc. of blood) and bloodflow (expressed as cc. blood per 100 cc. of hand). These estimations cannot be taken as absolute values because bloodflow was measured in the hand and blood gas determinations were made on blood drawn from the femoral vessels of the leg. However, venous oxygen values of blood obtained from the antecubital vein of the arm immersed in the plethysmograph corresponded closely with femoral vein blood values in Case 4. Bloodflow in the hand may not be an exact index of bloodflow in other parts of the body but may mirror the direction of change.[4] With these reservations in mind we have listed in Table 1 oxygen utilization (expressed as cc. oxygen per 100 cc. of hand per minute) and the mental state of the patients. These figures suggest that there is a marked reduction in oxygen utilization in untreated diabetic acidosis. The patients with most markedly decreased oxygen utilization were semiconscious or unconscious; those with less marked reductions were conscious. Treatment seemed to be accompanied by an increase in oxygen utilization.

Blood pressure was reduced in all patients on admission. The degree of reduction varied. The most seriously ill patients were unconscious and had the lowest blood pressures ranging from 50 to 96 mm. of mercury systolic over 30 to 70 mm. of mercury diastolic. The patients whose clinical condition was much better were conscious and had nearly normal blood pressures.

Initial determinations for serum proteins, hemoglobin and cell volume were elevated above recovery levels in all cases. These observations served to indicate the severity of the dehydration.

Serum protein concentrations decreased after the administration of parenteral fluids. In Cases 4, 5 and 6 proteins fell sharply during treatment and then increased somewhat during the recovery period. All of these patients received 6% acacia intravenously. Case 3 received acacia but failed to show any marked reduction of serum protein. The other cases showed a reduction of serum pro-

teins from the level on admission to that after hydration which was maintained after recovery.

Hemoglobin values fell during hydration. The levels after hydration were maintained. In Cases 4 and 5 the hemoglobin rose while the proteins fell during hydration. Both of these patients were seriously ill and both received acacia. Peters explained similar changes in his patients on the basis of continued loss of fluid containing protein. He found this in patients who were failing clinically. His patients did not receive acacia; ours did.

Cell volume by hematocrit paralleled the changes in hemoglobin.

All of these studies, except the peripheral bloodflow, were made on 11 additional patients with consistent results. These results were not included because oxygen capacity was calculated from hemoglobin values, the volumetric Van Slyke apparatus was used for the blood gas analyses and peripheral bloodflow was not measured. Although the number of cases reported is small, the findings are significant because of the consistency of the results in the 8 cases and the consistency of the group of 8 with the 11 preliminary cases.

**Discussion.** Our observations on the serum protein concentration, hemoglobin and cell volume by hematocrit in patients with diabetic acidosis agree with those of Peters *et al.*[15,16] They point to a severe dehydration and hemoconcentration. These patients had long periods of hyperglycemia and glycosuria resulting in diuresis preceding the acidosis. Atchley and his coworkers[3] found that withdrawal of insulin from diabetic patients produced an increase in the excretion of sodium, potassium and chloride with diuresis. This initial electrolyte loss occurred independently of the development of ketosis. They also found that after a longer period of insulin withdrawal there occurred an accumulation of ketone bodies which further depleted the stores of fixed base and when the alkali reserve depleted uncompensated acidosis developed.

Chang, Harrop and Schaub[5] showed that the dehydration of diabetic acidosis was accompanied by a reduction in blood volume. The acidosis in their cases was less severe than that found in those we studied. All of their cases were sufficiently conscious to cooperate in measurement of blood volume by the carbon monoxide method. Although their patients had relatively mild acidosis, the reduction in blood volume varied from 250 to 600 cc. If patients with relatively mild diabetic acidosis show a reduction of blood volume up to 600 cc., it is not unreasonable to believe that our patients in severe diabetic acidosis with associated peripheral circulatory failure would have more marked reduction in blood volume.

Cold extremities, rapid, thready, low volume pulse and low blood pressure, well-known characteristics of surgical shock, were seen in the patients in diabetic acidosis with peripheral circulatory failure. Freeman *et al.*[11] found that patients in surgical shock had marked

reduction in peripheral bloodflow. Dogs in which shock had been produced experimentally[8c,10] showed hemoconcentration, reduced blood volume and peripheral bloodflow. The increased hemoglobin, serum protein concentration and cell volume in our patients indicated the extent of the dehydration and hemoconcentration and suggested the probable existence of a reduced blood volume. Measurements of the bloodflow through the hand indicated the severity of reduction in the peripheral circulation. These observations indicate that our patients like those in surgical shock have peripheral circulatory failure. A suggested mechanism for the production of peripheral circulatory failure in diabetic acidosis is summarized in Figure 4. The vicious circle leading to peripheral circulatory failure has been adapted from Freeman's paper.[8b]

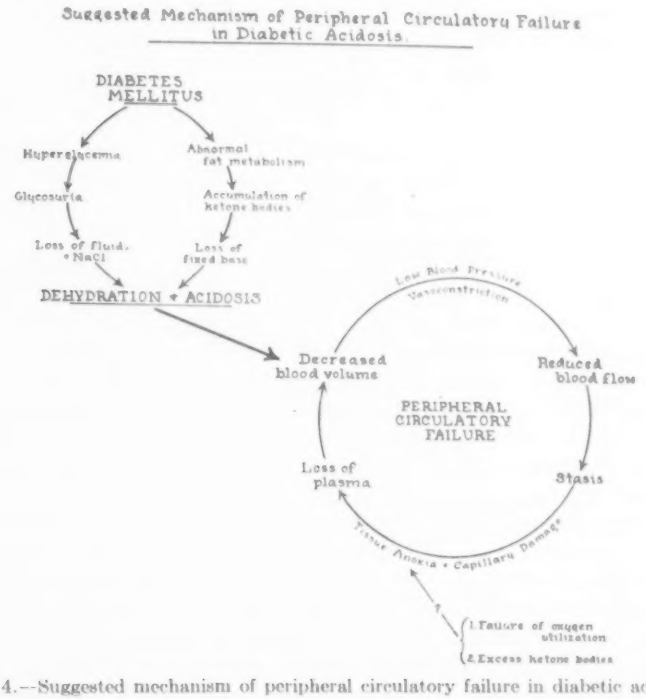


FIG. 4.—Suggested mechanism of peripheral circulatory failure in diabetic acidosis.

Blood gas analyses in surgical shock[11] show a widening of the arteriovenous oxygen difference with a marked reduction in venous oxygen saturation. This reduced venous oxygen content is regarded as the result of reduced circulation; the tissues having obtained as much oxygen as possible from the blood delivered at a markedly reduced rate of speed. When the reduction in bloodflow is so great, that even very complete removal of oxygen from the blood arriving

fails to deliver an adequate oxygen supply per unit of time, tissue anoxia results. This is the stagnant type of anoxia of surgical shock.

Patients in diabetic acidosis, however, were found to differ from those in surgical shock with respect to the level of their venous oxygen saturation in the presence of markedly reduced bloodflows. Figure 5 compares the bloodflow, arterial and venous oxygen saturation in the patients with peripheral circulatory failure in diabetic

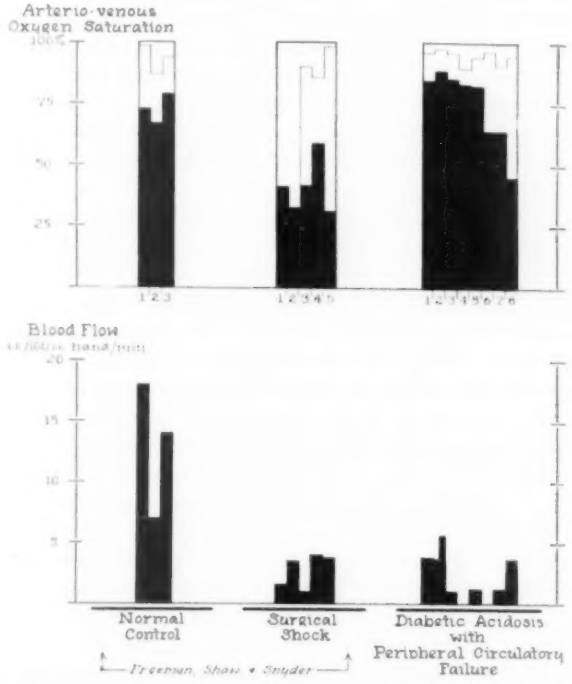


FIG. 5.—Comparison of bloodflow and venous oxygen saturation in diabetic acidosis with normal controls and surgical shock. Each column represents one case, as indicated by the numbers beneath the upper row.

acidosis with normal controls and patients in surgical shock studied by Freeman, Shaw and Snyder.[11] Reductions of peripheral bloodflow of the magnitude found in surgical shock were found in the patients with diabetic acidosis. Venous blood leaving such regions of reduced bloodflow, however, showed little oxygen unsaturation. The reduced peripheral bloodflow indicated the reduction in speed of arrival of hemoglobin bringing oxygen to the tissues. The high venous oxygen saturation suggests a failure of the hemoglobin to liberate its oxygen to the tissues or a failure of the tissues to remove the oxygen which does arrive. These findings point to the existence of a histotoxic as well as a stagnant anoxia in the peripheral circulatory failure of diabetic acidosis.

Conclusions concerning oxygen utilization in any one part of the body cannot be made with assurance unless the bloodflow and arteriovenous oxygen differences are measured in the same part. In these experiments bloodflow measurements were made on the hand, represent chiefly skin bloodflow and are not a measure of bloodflow in visceral organs. Venous blood gas analyses were made on blood drawn from the femoral vein. This blood consists of venous return from both superficial and deep leg tissues. However, evidence has been obtained suggesting that the estimated results of oxygen utilization obtained would not be altered greatly if blood gases and bloodflow had been measured in the same part. In Case 4, blood drawn from a superficial antecubital vein in the arm in the plethysmograph had a venous oxygen content very close to that obtained on femoral vein blood during acidosis and after recovery.

Results calculated from arteriovenous oxygen difference and bloodflow suggest that there is a decrease in the ability of the tissues of patients with untreated diabetic acidosis to utilize oxygen. The degree of reduction of oxygen utilization may be correlated with the mental state of the patient. Treatment is accompanied by an apparent increase in tissue oxygen utilization. The levels reached during treatment are greater than recovery levels and indicate possible repayment of an oxygen debt. Speculation concerning possible causes for a failure of oxygen utilization in diabetic acidosis centers around: 1, inability to utilize carbohydrate; 2, ketosis, or 3, acidosis. Any one, or all three, may be responsible for the findings.

The reduction in circulation which all of our patients showed in varying degrees was present before treatment was started and was an integral part rather than a late complication of the diabetic acidosis. When there was a moderately reduced peripheral bloodflow but with maintained blood pressure (Fig. 1) saline solution given by hypodermoclysis was sufficient to increase the bloodflow, to maintain the blood pressure and to correct the dehydration. It may be inferred that the blood volume was restored and maintained by this form of treatment alone.

When there was a more marked reduction in peripheral circulation, a low blood pressure and unconsciousness (Figs. 2 and 3), saline or other solutions of electrolytes without colloid osmotic pressure, when administered either by hypodermoclysis or by the intravenous route, seemed to be insufficient to bring about a permanent increase in bloodflow and blood pressure or to restore the blood volume. It seemed as though the reduced peripheral circulation did not absorb fluids given by hypodermoclysis. Again, it is probable that the vascular system in peripheral circulatory failure cannot retain osmotically inactive fluids. Finally, it is recognized that saline brings about a temporary increase but does not maintain

the blood volume (Freeman and Wallace[9]). For these patients in peripheral circulatory failure adequate volumes of osmotically active solutions such as plasma, blood or acacia should be given early by the intravenous route and should be continued until bloodflow and blood pressure are increased and maintained. Saline given simultaneously or subsequently for the replacement of electrolytes and water will then probably be effectively absorbed and retained.

The results of these studies lead us to believe that the prompt restoration of blood volume is almost as important as the administration of insulin in the treatment of diabetic acidosis. Even though lack of insulin be the initiating factor in the series of events leading to the development of diabetic acidosis with peripheral circulatory failure, in treatment measures directed toward restoration of blood volume and adequate circulation should be instituted before or simultaneous with the administration of insulin.

**Summary and Conclusions.** 1. Eight patients with diabetic acidosis were studied. Initially elevated hemoglobin, hematocrit and serum protein with a decrease following administration of fluids showed the presence of dehydration and hemoconcentration.

2. Peripheral bloodflow in the hand, as measured by the plethysmograph was reduced.

3. Venous oxygen saturation was high in the presence of marked reductions in peripheral bloodflow.

4. Physiologic evidence presented supports the clinical impression of the existence of peripheral circulatory failure in diabetic acidosis.

5. The existence of an unusually high venous oxygen saturation in the presence of a reduced peripheral bloodflow suggests a failure of oxygen utilization by the tissues. Possible causes suggested for the failure of oxygen utilization are: 1, inability to utilize carbohydrate; 2, ketosis, or 3, acidosis.

6. These findings point to the existence of a histotoxic as well as a stagnant anoxia in the peripheral circulatory failure of diabetic acidosis.

7. The importance of the prompt restoration of blood volume and the maintenance of adequate circulation in the treatment of diabetic acidosis is stressed.

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## THE RESULTS OF SULPHOCYANATE THERAPY IN HYPERTENSION.

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Potassium sulphocyanate therapy was first employed in the Cardiology Department of the Wisconsin General Hospital in certain selected cases of hypertension in 1929. A much broader application of this type of treatment was made possible by Barker's announcement in 1934 of a method for determining the blood cyanates and this form of laboratory control has been used routinely since June, 1935. The experience in a group of 50 cases has been so satisfactory that it seemed advisable to report the results obtained in this series, particularly in view of the current controversy over the propriety of administering thiocyanate to patients with hypertension.

Barker's original publication[1a] presenting his method of treating hypertension with potassium sulphocyanate contained a comprehensive review of the literature up to March, 1936. A few of the authors mentioned in his bibliography had been favorably impressed with the results of this drug but the majority of the writers were opposed to it on the grounds that the effective dosage was sufficiently toxic to produce unpleasant and sometimes dangerous side reactions. Barker, in his paper, presented a method of administering thiocyanate which was both effective and safe provided proper laboratory control was available. He described a relatively simple technique for the determination of the blood cyanate. His patients were given from 0.3 to 1 gm. of potassium sulphocyanate daily for

a number of days until the blood cyanate reached a level of from 8 to 10 mg. per 100 cc., at which time the dose was reduced to a point which would maintain the blood cyanate somewhere in the therapeutic range which was found to vary between 6 and 12 mg. per 100 cc. Of the 45 patients reported in his series, 35 obtained a distinct drop in the blood pressure and definite relief from their symptoms. It was pointed out that the toxic range lay well above 15 mg. and that serious complications and fatalities probably occurred only when the level reached 40 to 50 mg. Untoward symptoms were avoided by so regulating the dose as to maintain the blood cyanate well below the toxic level and within the therapeutic range. In January, 1937, Barker[15] published a second paper in which he reviewed and brought up to date the data presented in his original article. Later in that year Griffith, Lindauer and Campbell[6] reported a series of 26 hypertensive patients treated with thiocyanate after the method of Barker. They encountered no fatalities and no major complications. Of 16 patients adequately treated and controlled, they obtained good results in 10. They presented a micro-modification of Barker's method for determining the blood cyanate using standards made of colored ink. This method required only a few drops of blood which could be obtained by puncturing the finger and avoided the necessity of drawing blood from a vein. Steidl and Steenken[11] administered potassium sulphocyanate to 3 patients with pulmonary tuberculosis and hypertension. A definite reduction in the blood pressure was obtained in all 3 cases and in none was there any evidence of deleterious effects so far as the tuberculosis was concerned. Massie, Ethridge and O'Hare[8] gave sodium sulphocyanate to a series of 14 ambulatory hypertensive patients and made a special effort to eliminate as far as possible all psycho-therapeutic effects. The blood cyanate was maintained between 5 and 7 mg. per 100 cc., and a lowering of the blood pressure was obtained in every case. No changes in the renal function were noted, there was no tendency to develop anemia, the ophthalmoscopic findings showed no alteration and serial electrocardiograms, taken on a few of the patients, showed no deviation from the controls. A variety of untoward symptoms were noted, including skin eruptions, nausea, vomiting, diarrhea, mental confusion and precordial pain but no serious complications were encountered. These authors concluded that patients treated by this method should be carefully selected and closely observed, and that proper control of dosage was necessary in each individual case according to the cyanate level in the blood. More recently, Wald, Lindberg, and Barker[12] reviewed the toxic manifestations encountered in cyanate therapy. They admitted that the thiocyanates were toxic and stated that their beneficial action in reducing blood pressure depended to a certain extent on their peculiar toxicity. For the most part, the toxic symptoms were mild

when the blood cyanate was kept at a safe level and became severe only when the amount of cyanate in the blood became definitely elevated. No patient who had previously experienced angina pectoris suffered a greater degree of angina during potassium sulphocyanate therapy, although they felt certain that in a few cases angina had developed as a direct result of the hypotensive action of the drug. No alterations in the electrocardiogram were noted. Garvin[4] reported a fatal case in which the toxic manifestations of the thiocyanate appeared while the blood level was supposedly in the non-toxic range and death was thought to be due to an idiosyncrasy to the drug. He concluded that since such intolerance cannot be recognized in advance, thiocyanate therapy must be considered dangerous. Robinson and O'Hare[10] published the results of their experience with a series of 75 patients treated with thiocyanates which in general paralleled those of Barker. Mosenthal,[9] in reviewing the medicinal treatment of hypertension, stated: "There is no doubt that the cyanates in sufficient doses will lower blood pressure and relieve symptoms of hypertension, though their administration is associated with considerable danger." But he added: "Control of the thiocyanate administration by quantitative determination of the cyanates in the blood, as suggested by Barker, is a distinct advance in this therapy. The original conclusion of Barker that the optimal therapeutic level ranges between 7 and 12 mg. per 100 cc. of blood and that higher concentrations may be associated with toxic manifestations has been verified and furnishes an excellent guide to the rational use of the cyanates."

Current Comment[2] has recently called attention to several unfavorable reports regarding the sulphocyanates, including the one by Garvin,[4] and concluded: "The value of sodium or potassium thiocyanate, in the light of its dangerous possibilities, seems more doubtful than ever."

It is obvious from the controversial nature of the foregoing references that the advisability of administering thiocyanates for the control of hypertension is still a moot question. It can be settled only through further experience and by the reporting of results obtained by physicians dealing with this problem.

**Present Series.** During the past 11 years 50 patients consisting of 21 males and 29 females with "essential hypertension" have been treated with potassium sulphocyanate in the Cardiology Department of this hospital.* With one or 2 exceptions all were ambulatory throughout the period of observation. The important characteristics of the group have been summarized in Table 1. The age of the patients ranged from 16 to 78 years (average, 51). In the 39 cases in which hypertension had been diagnosed previous to their being seen in the Cardiology Department, the known duration

* We are indebted to Dr. M. J. Lustok of Milwaukee for the follow-up data on one of the patients who originally belonged to this series.

of the condition varied from 1 month to 25 years with a mean of 5 years. Evidence of hypertensive, rheumatic or coronary heart disease was found in 30 patients and signs of renal involvement were present in 19. Arteriosclerosis was relatively common. Other complications such as diabetes, glaucoma and food allergies occurred less frequently. The systolic blood pressure after a period of stabilization and prior to starting sulphocyanate therapy, ranged from 155 to 245 mm. of mercury with a mean of 197 for the entire group. The diastolic pressure ranged from 90 to 145 with a mean of 115.

TABLE 1.—PRESENT SERIES.

| | Males. | Females. | Total. |
|---|---|---|---|
| Number of cases | 21 | 29 | 50 |
| Age in years: | | | |
| Range | 16–65 | 38–78 | 16–78 |
| Average | 49 | 53 | 51 |
| Known duration of hypertension in 39 cases: | | | |
| Range | 3 mos.–13 yrs. | 1 mo.–25 yrs. | 1 mo.–25 yrs. |
| Average | 4.3 yrs. | 5.8 yrs. | 5.1 yrs. |
| Number of cases treated under laboratory control | 18 | 25 | 43 |
| Number of patients with heart disease | 15 | 15 | 30 |
| Number of patients with renal involvement | 11 | 8 | 19 |

**Method.** In practically every case the patient was observed over a period of at least 3 months, and in many instances for one or more years, during which the usual hygienic measures were instituted and various types of treatment employed, including vasodilators, potassium iodide and sedatives such as bromides and barbiturates. Blood pressure readings were taken at frequent intervals and it was not until after the arterial tension had become relatively stabilized under this sort of a regimen that potassium sulphocyanate therapy was begun.

The drug was administered in an aqueous solution* containing 5 grains to the dram and the patient started on a dose of 1 dram (5 grains) 2 or 3 times a day. The blood cyanate was determined at weekly intervals and the initial dose continued until the therapeutic level of 6 to 12 mg. per 100 cc. was reached. The amount was then reduced and a maintenance dosage was determined for each individual patient such that the blood cyanate was kept within the therapeutic range at the level which appeared to produce the optimum blood pressure response. After the first few weeks, blood samples were taken at approximately monthly intervals, and in some cases even less frequently.

It should be emphasized that no attempt was made to force an excessively high blood pressure down to a normal level, but simply to reduce the tension below the danger range and thus relieve the excessive strain on the heart, kidneys and cerebral vessels.

**Results.** *Subjective Improvement.* The degree of subjective improvement is given in Table 2. Four of the patients had experienced none of the usual hypertensive symptoms but of the 46 who

* Recently some patients have been receiving enteric-coated tablets containing 3 grains of potassium sulphocyanate supplied through the courtesy of the Eli Lilly Company of Indianapolis. These have proved highly satisfactory and, for the most part, have been preferred by the patients.

complained of headaches, dizziness, tinnitus, easy fatigue and other distressing sensations commonly associated with hypertension, 13 (28%) reported practically complete relief from their symptoms and were rated as showing *excellent* subjective improvement. The results were considered *good* in 16 (35%), *fair* in 9 (20%), while relatively little or no improvement was noted in 6 (13%). Grouping the *excellent* and *good* results together, approximately 63% felt definitely better while taking cyanate. Six patients tolerated the drug poorly as evidenced by precordial pain in 1, a skin rash in 3 and a skin rash combined with falling hair in 2. One patient complained of nausea at first, but this was of short duration and did not prevent continuance of the treatment. The most serious toxic reaction encountered occurred in a woman of 68 who became mentally confused and went into a state of physical collapse in spite of the fact that the blood cyanate did not exceed the accepted therapeutic level. During the course of the next 3 years, two subsequent attempts were made to administer cyanate because of a dangerous and uncontrollable rise in the arterial tension, but a repetition of the toxic reaction on both occasions made it necessary to abandon this form of therapy. Another patient, a woman of 38, did not feel as well while taking the drug, and although the blood pressure response was fairly satisfactory, cyanate had to be discontinued.

TABLE 2.—DEGREE OF SUBJECTIVE IMPROVEMENT.

| | No. of cases. | %. | |
|---|---|---|---|
| Excellent | 13 | 28 | 63 |
| Good | 16 | 35 | |
| Fair | 9 | 20 | 37 |
| Poor or none | 6 | 13 | |
| Worse | 2 | 4 | |
| Total | 46* | 100 | |

* Four of the group of 50 patients experienced no hypertensive symptoms.

*Objective Improvement.* The results with respect to objective improvement are summarized in Table 3. The degree of improvement was judged largely on the drop in the blood pressure, although other factors such as reduction in the degree of cardiac dilatation and disappearance of congestive failure were also taken into consideration in grading the results. The response was considered *excellent* if a moderately high blood pressure could be controlled at or below 150 systolic and 90 diastolic. The results were judged as *good* if a systolic level of 160 to 170 and a diastolic level of 100 or slightly over could be maintained. Lesser responses were graded as fair or poor, depending upon the individual circumstances. Classification into these various grades was modified to a certain extent by the height of the original blood pressure level and the number of millimeters of mercury through which the pressure dropped. In one man, who, previous to treatment, had been carry-

ing a tension of 245/145, the reading fell to 180/110 with cyanate therapy and the result was considered *good*. In another patient whose pressure dropped from 190/115 to 175/110, the result was considered *poor*.

TABLE 3.—DEGREE OF OBJECTIVE IMPROVEMENT.

| | No. of cases. | %. | |
|---|---|---|---|
| Excellent | 24 | 48 | 78 |
| Good | 15 | 30 | |
| Fair | 8 | 16 | 22 |
| Poor | 3 | 6 | |
| Total | 50 | 100 | |

Referring to Table 3, it will be noted that objective improvement was considered excellent in 48% of the series, good in 30%, fair in 16% and poor in 6%. Some degree of reduction was obtained in every case, but satisfactory results, grouping the *excellent* and *good* responses together, were noted in 78%. In the remaining 22% the results were more or less disappointing, but in only 6% were they practically *nil*.

*Blood Pressure Response.* The actual drop in the blood pressure for the entire group will be found in Table 4. The level at which each patient stabilized during the preparatory period was noted and the range for the group as recorded under the heading "Before KCNS" was 155 to 245 systolic and 90 to 145 diastolic. The mean for the entire series was 197 systolic and 115 diastolic. The level at which the blood pressure could be maintained by adequate doses of cyanate was determined from a large number of readings in each case and the results for the group have been listed under the heading "With KCNS." The systolic pressure under treatment varied from 130 to 210 with an average of 156 and the diastolic varied from 70 to 130 with an average of 94. This represents an average drop of 41 mm. of mercury in the systolic pressure and 21 mm. in the diastolic pressure.

TABLE 4.—EFFECT OF POTASSIUM SULPHOCYANATE ON THE BLOOD PRESSURE.

| | Before KCNS. | With KCNS. | Net change. |
|---|---|---|---|
| Systolic B.P. in mm. Hg: | | | |
| Range | 155–245 | 130–210 | |
| Average for group | 197 | 156 | −41 |
| Diastolic B.P. in mm. Hg: | | | |
| Range | 90–145 | 70–130 | |
| Average for group | 115 | 94 | −21 |

In most instances the blood pressure remained lowered only as long as the blood cyanate was maintained at a certain minimum level, but in 4 patients who had been known to have hypertension for 1 to 2½ years, and in 1 where the previous duration was unknown, the blood pressure remained within the normal range for months

or years after the cyanate was discontinued. However, one is not warranted in holding out cyanate therapy as a possible "cure" for hypertension as such results have been decidedly the exception rather than the rule.

*Optimum Blood Cyanate and Maintenance Dosage.* As noted by Barker,[1a] the therapeutic range for the blood cyanate seemed to lie between 6 and 12 mg. per 100 cc. although in rare instances good results were obtained with the blood cyanate as low as 4 mg. and in 4 cases levels of 13 to 16 mg. were necessary to obtain a significant lowering. Judged on the basis of the combined subjective and objective response the optimum blood cyanate level was estimated for each patient and the mean for the entire group was found to be 8.3 mg. per 100 cc.

Rather marked variation was noted in the dosage of potassium sulphocyante needed to maintain the blood cyanate at the desired level in the individual case. A few patients required as little as 3 or 4 5-grain doses per week while others were found to need as many as 14. In one instance the requisite maintenance amount was 21 5-grain doses a week. Ten doses per week was found to be adequate for over a third of the patients and the average for the entire series was 9.

Blood counts, urinalyses and electrocardiograms showed no significant changes during the course of cyanate therapy. Serial orthodiagrams revealed a distinct tendency of the frontal area of the cardiac shadow to decrease as the blood pressure dropped. Results of this phase of the study will be reported in detail in a future communication.

*Sympathectomy.* Two patients were subjected to bilateral thoracic sympathectomy after having been given thorough trials of cyanate therapy. The first patient, a man of 51, whose blood pressure was 200/120 before commencing treatment, was controlled for a time at a level of 165 to 180 systolic and 105 to 110 diastolic, but in April, 1939, it became necessary to reduce the dose of thiocyanate due to the appearance of a skin rash, and the tension returned promptly to its previous level. In view of the fact that the response to treatment had not been satisfactory and that full doses of potassium sulphocyanate were no longer tolerated, sympathectomy was advised. On May 24, 1939, bilateral supradiaphragmatic sympathectomy was performed by Dr. Loyal Davis of Chicago and for a few days thereafter the blood pressure was 120/72. During the next 2 or 3 weeks the tension gradually climbed to 180/110 at which the potassium sulphocyanate was resumed. The blood pressure promptly dropped to 150/100 where it remained for 5 months. At this time the patient's wife developed cancer and under the resulting nervous strain, the systolic pressure ranged from 170 to 180 and the diastolic from 100 to 110. After successful surgical removal of the wife's cancer, the patient's blood pressure

has again come under control in the neighborhood of 150/100, he has been entirely symptom-free, and the skin rash has not recurred.

The second patient, a nurse of 42 years, had been taking potassium sulphocyanate with good results for 2 years but then developed a skin rash. Sympathectomy was advised in the hope that even if the operation failed to effect a permanent reduction in the blood pressure, smaller doses of thiocyanate might be employed successfully afterward without the production of a dermatitis. Extensive sympathectomy was performed on September 5, 1940, and for several days thereafter the blood pressure remained around 130/80. About 3 months later the patient returned to active nursing duty and has been working ever since. At the present time, 7 months after operation, she feels better than she has in years, the blood pressure remains at a relatively normal level and there has been no indication for the resumption of cyanate to date. It is recognized, however, that more time will have to elapse before the actual results of the sympathectomy can be accurately evaluated in this case.

*Mortality.* During the 11 years covered by this study, 4 patients in the series died of congestive heart failure, 4 of cerebral hemorrhage, 1 of coronary occlusion and 2 of pneumonia. In no instance could death be attributed in any way to the thiocyanate. In fact, none of the 9 patients who died of their cardiovascular disease had been taking cyanate for 1 or more months preceding death. One man of 43 who had shown an excellent response to cyanate therapy felt so well that he discontinued treatment of his own accord. One month later the blood pressure rose to 170/130 and a fatal cerebral hemorrhage occurred. A banker, 45 years of age, who was fairly well controlled over a period of 8 months on potassium sulphocyanate voluntarily discontinued the drug during the fall of 1937 and in January, 1938, suffered a subarachnoid hemorrhage which incapacitated him for several weeks. He was readily persuaded to resume cyanate therapy after he had recovered and was faithful to the treatment for about 9 months. At this time he decided to discontinue cyanate and give a garlic and parsley preparation a trial. He did not again return for observation and about 1 year later was reported to have died of a cerebral hemorrhage. Judging from the mortality experience furnished by this limited series, it would appear that a hypertensive patient is actually safer while taking cyanate in adequate doses, for in no instance did a patient die while taking the drug. Moreover, in only one instance did a cerebral hemorrhage occur while a patient was taking cyanate and this happened in one of the few patients whose blood pressure responded very poorly to treatment. Obviously, it is impossible to draw any definite conclusions as to the ability of cyanate therapy to prolong the life of a hypertensive patient as there is no way of knowing how long the patient would have lived without treatment; but the

authors have obtained the clinical impression that cyanate does postpone heart failure and cerebral accidents and thus tends to prolong life in those patients who respond well to therapy.

**Case Reports.** CASE 1.—J. M., a 55-year-old white male, was first seen in the Cardiology Department, October 9, 1936. He had been known to have high blood pressure for the past 11 years and, during this period, had experienced temporal and occipital headaches which usually came on right after breakfast and lasted all day. They had occurred only infrequently for several years but recently had been present every day and were becoming almost unbearable.

On physical examination the pulse was regular at the rate of 72 and the blood pressure was 210/110. Systolic murmurs were present at the mitral and aortic areas. There was no evidence of congestive failure.

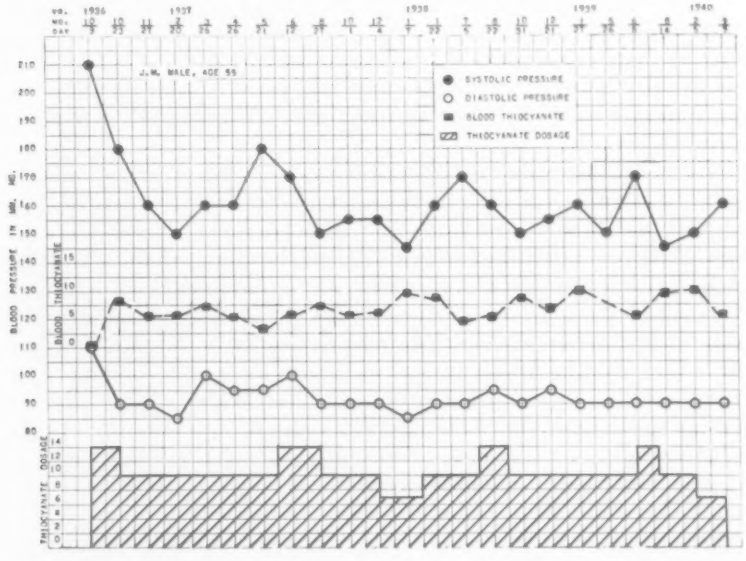


CHART 1.—Clinical course in Case 1, a 55-year-old white male. Had suffered from hypertension and severe headaches for 11 years. Symptoms were completely controlled by thiocyanate therapy. Chart covers a period of 4 years and is composed of representative readings obtained at intervals. The thiocyanate dosage is graphed as number of 5-grain doses per week.

Orthodiascopic examination revealed moderate dilatation of the aorta and moderate enlargement of the left ventricle. The electrocardiogram showed the typical pattern of left ventricular strain.

The following diagnosis was made: hypertensive heart disease, moderate cardiac enlargement, moderate dilatation of the aorta, advanced myocardial degeneration, marked hypertension, relative mitral regurgitation and diabetes mellitus.

Since the patient was known to have had hypertension for at least 11 years and in spite of various types of treatment had continued to suffer from severe headaches, he was immediately started on potassium sulphocyanate and was given 5 grains twice daily for 2 weeks after which he was maintained on a dose of 5 grains 10 times weekly. The headaches com-

pletely disappeared after 3 weeks and did not recur for a period of 2 years. During the past 2 years there has been a tendency for the headaches to return although they have not been nearly as severe nor as frequent as previously. Strangely enough the recurrence of the headaches has not been accompanied by a rise in blood pressure. This patient's course is shown graphically in Chart 1 and it will be seen that his systolic pressure has been maintained at an average of 160 and the diastolic in the neighborhood of 90. The blood cyanate has ranged for the most part between 5 and 10 mg. per 100 cc. This man has remained ambulatory and serial orthodiagrams have shown no increase in the heart size. In February, 1940, he went through an attack of lobar pneumonia from which he made an uneventful recovery. The cardiac reserve has remained low but there has never been any evidence of frank congestive failure.

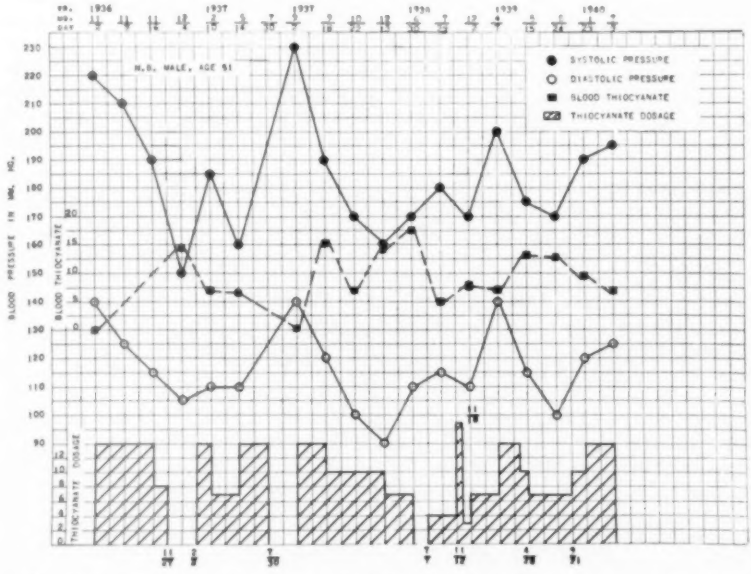


CHART 2.—Clinical course in Case 2, a 51-year-old white male. Graph illustrates an excellent initial response to therapy and a definite rise in blood pressure whenever the drug was temporarily discontinued. A satisfactory response was always obtained with resumption of therapy.

CASE 2.—N. B., a Jewish clothing store owner, of 51, was first seen on November 2, 1936. He was known to have had high blood pressure for 13 years but felt fairly well until 5 weeks before admission when he was seized with marked shortness of breath, expectoration of frothy sputum and a feeling of pressure in the chest. He was taken to a hospital and given oxygen which relieved the attack in 4 hours. One week later he had a second attack following which he was confined to the hospital for 10 days. In spite of remaining at complete bedrest, he had suffered three similar but less severe attacks in the meantime.

Physical examination revealed obesity, marked dyspnea while sitting quietly in a chair, definite alternation of the pulse, blood pressure 215/140, moderate enlargement of the heart, gallop rhythm and an enlarged and tender liver.

Orthodiascopic examination confirmed the clinical impression of moderate cardiac enlargement. The electrocardiogram showed the characteristic pattern of left ventricular strain with depression of the $S$–$T$ segments and inversion of the $T$ waves in Leads I and II.

A diagnosis was made of hypertensive heart disease, moderate cardiac enlargement, marked hypertension, congestive failure, functional capacity IV. Since he had been at complete rest for the past 3 weeks with very little improvement, he was immediately started on potassium sulphocyanate and given 5 grains twice daily. This dose was continued for 2 weeks at which time the blood cyanate had reached 14 mg. per 100 cc. and the blood pressure had dropped to 190/115. The patient improved rapidly both subjectively and objectively and by maintaining the blood cyanate at a level of 12 to 15 mg. it has been possible to keep the systolic pressure between 160 and 180 and the diastolic pressure between 105 and 110. After a few weeks, the gallop rhythm and the pulsus alternans disappeared, the patient went back to work and has been putting in a full day at his store ever since. He has never had a recurrence of the paroxysmal dyspnea during the 4 years and subjectively has felt as well as ever. On one occasion he discontinued the potassium sulphocyanate of his own accord for about a month and the blood pressure rose to 230/140. Resumption of the cyanate promptly restored the blood pressure to its former level (see Chart 2).

This man still runs a moderate hypertension but the blood pressure has been kept out of the danger range for a period of 4 years during which time he has been practically free from symptoms and has been able to carry on his business. There is no doubt in the minds of the various physicians who observed him in 1936 that he would have died in a short time had not the blood pressure been brought under control. It seems fair to assume that through the agency of potassium sulphocyanate, this patient has been given at least 4 additional years of life during which he has been free from discomfort and able to support his family.

Case 3.—A. H., a woman of 48, employed as an office secretary, was referred to the Cardiology Department May 17, 1933. Hypertension had been discovered 3 years previously and she had been suffering from frequent severe vertical headaches coming on during the night or early morning and lasting most of the day. The systolic pressure had ranged from 150 to 180 and the diastolic from 100 to 120.

The family history was significant in that the mother and father had both died of cerebral hemorrhage and 1 brother and 1 sister were known to have hypertension. (Both the brother and sister, neither of whom were treated with cyanate, have since died of "strokes" while patient has been under observation.)

On physical examination the pulse was regular at a rate of 86 and the blood pressure varied from 185 to 200 systolic and from 120 to 130 diastolic. The heart was slightly enlarged and the aortic second sound had a "bottom-of-the-well" quality. There was no evidence of congestive failure.

Orthodiascopic examination revealed slight dilatation of the aorta and moderate cardiac enlargement. The electrocardiogram was normal except for a deep $Q$ wave in Lead III.

Barker's method of laboratory control was not available at this time and the patient was given 2 grains of potassium sulphocyanate 3 times daily for 2 weeks during which the blood pressure dropped to 130/90 and the headaches completely disappeared. During the next 3 years the patient continued to take this dose of potassium sulphocyanate for 2-week periods with intervals of several weeks between courses. Since July 31, 1936, she has taken a maintenance dose of 5 grains of this drug 10 times weekly which has kept the blood cyanate in the neighborhood of 5 to 6 mg. per

100 cc. and has controlled the blood pressure at an average level of 135/90. She has been entirely free from headaches during this time. In October, 1938, the blood pressure was 125/80 and the drug was discontinued temporarily. Six weeks later the blood pressure was found to be 160/105 but the headaches had not returned. The cyanate was resumed and the blood pressure has been controlled in the region of 140/95 ever since. The clinical course is illustrated in Chart 3.

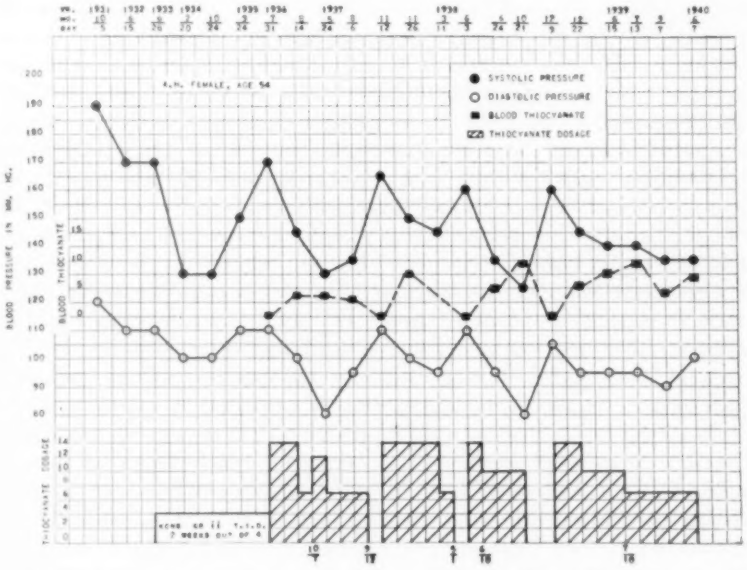


CHART 3.—Clinical course in Case 3, a 54-year-old white female. Patient has been under treatment with thiocyanate for 9 years. Blood pressure has been satisfactorily controlled on 7 to 10 5-grain doses per week.

**Discussion.** Notwithstanding the monumental experiments of Goldblatt,[5] dealing with the production of hypertension in dogs and the numerous elaborate studies which have been inspired by his work, the problem of the etiology and mechanism of "essential hypertension" in man is still not clearly understood. As a result there is a great diversity of opinion among leading authorities as to whether one is ever justified in attempting to reduce an elevated blood pressure. Those who take the negative side of the question oppose treatment on the grounds that hypertension is a compensatory mechanism necessitated by a pathologic reduction in circulation to some tissue or organ and that a lowering of the arterial tension will result in a deficient blood supply to the tissue or organ involved. On the other hand, many eminent clinicians feel that an excessively high blood pressure, uncontrolled over a period of years, in most instances leads to heart failure, cerebral hemorrhage or uremia and premature death, and that if a moderate reduction of the blood pressure can be effected, the degenerative process can be retarded

and life prolonged possibly for a number of years. To those who believe in actively treating and reducing an elevated blood pressure, potassium thiocyanate offers an effective weapon which can be depended upon to afford both subjective and objective relief in the majority of cases.

It must be remembered that thiocyanate is a toxic drug and cannot be employed indiscriminately. It should never be given unless laboratory control is available and both doctor and patient are willing to take the trouble of having the blood cyanate checked at regular intervals. The individual variation in the susceptibility and response of patients is so marked that the optimum blood cyanate level and the dosage necessary to maintain this level have to be determined for each case. Treatment should not be offered to any patient who is not willing to coöperate fully and report for blood cyanate determinations at frequent intervals until his optimum dose has been determined. Except in rare instances the margin of safety between the therapeutic and toxic range is sufficiently wide to enable one to easily avoid any serious reactions due to the drug itself if reasonable care is exercised. Minor complications such as skin rashes, falling hair and mild aching of the muscles, particularly those of the thigh, may be expected in approximately 10% of the cases, but only infrequently will it be necessary to discontinue treatment permanently. Organic heart disease and even fairly marked degrees of renal impairment have not proved to constitute contraindications to the drug. However, it has been found that patients who have suffered a cerebral accident do not respond well to this type of therapy.

We feel compelled to take issue with the conclusions expressed in a paragraph entitled, "Hypertension and the Thiocyanates" (in Current Comment of the *J. Am. Med. Assn.*[2]). Referring to Garvin's paper[4] the statement was made that, "A recent communication revealed eight fatalities reported as following the intake of thiocyanate." An analysis of Garvin's paper shows that of 7 fatal cases collected from the literature, 3 of the patients were not under treatment with the drug but took large amounts with suicidal intent. It is hardly fair to include such cases as an argument against the therapeutic use of a drug. In the case which Garvin himself reported, cyanate intoxication could probably have been avoided had the principles and methods advocated by Barker been more closely followed. Terminally, there was clinical evidence of bronchopneumonia which was confirmed at autopsy. It is perfectly possible that the pulmonary infection rather than the cyanate intoxication may have been the actual cause of death.

Current Comment[2] also stressed the findings of Hamilton *et al.*,[7] who had observed the effect of sodium thiocyanate on the blood pressure of hypertensive dogs. These investigators had observed a definite fall in pressure following administration of this drug, but

attributed the results to weather changes, and concluded that, "Cyanate did not produce a significant permanent lowering of the blood pressure in hypertensive dogs." Unfortunately, the crucial figures were lacking from their published data and the conclusions drawn were not warranted by the material presented. We strongly question whether Current Comment, on the basis of the material on which it predicated its opinion, can justify the implication that thiocyanate is too dangerous a drug to use clinically and possibly should be abandoned. No one will deny that the sulphocyanates are more or less toxic, but if the dose is intelligently regulated through adequate laboratory control as previously described, therapy can be extremely valuable and relatively safe.

The present outlook for combined sympathectomy and cyanate therapy is somewhat promising for those cases which do not respond to cyanate alone, but considerably more time and experience will be required to determine the value of this rather radical procedure.

**Summary and Conclusions.** During the past 11 years 50 patients with essential hypertension have been treated by the authors with potassium sulphocyanate. Barker's method of laboratory control has been employed routinely since June, 1935.

Subjective improvement as estimated by the disappearance of headaches, dizziness, tinnitus, and so on, was very definite in 63%, fair in 20% and disappointing in 17%. Six patients exhibited poor tolerance for cyanate as evidenced by precordial pain in 1, skin rash in 3 and skin rash combined with falling hair in 2. In addition, there were 2 other patients who felt distinctly worse while under treatment. One of these was apparently very sensitive to thiocyanate and treatment had to be abandoned because of mental confusion and physical collapse even with the blood cyanate in the accepted therapeutic range.

Some degree of reduction of the blood pressure was obtained in every case and objective results were considered satisfactory in 78%, fair in 16% and poor in 6%. The average systolic pressure for the entire group dropped from 197 before treatment to 156 with treatment while the average diastolic pressure dropped from 115 to 94. In 4 instances the blood pressure remained normal for months or years after discontinuing thiocyanate.

The optimum blood cyanate level ranged from 4 to 16 mg. per 100 cc. with an average of 8.3 mg. The maintenance dose of potassium sulphocyanate varied from 3 to 21 5-grain doses per week, with an average of 9 doses per week.

Extensive sympathectomy was performed in 2 cases but insufficient time has elapsed to properly evaluate the results.

During the 11-year period of observation 4 patients died of heart failure, 4 of cerebral hemorrhage, 1 of coronary occlusion and 2 of pneumonia. In no instance could death be attributed either directly or indirectly to cyanate administration.

Three illustrative cases have been described briefly.

Potassium sulphocyanate is regarded by the authors as a valuable drug in the treatment of hypertension and, properly employed, capable of prolonging life and preventing disability in a substantial percentage of patients suffering from this condition.

Potassium sulphocyanate can be safely administered provided proper laboratory control is exercised at all times.

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## CONGENITAL HEART DISEASE DURING PREGNANCY.

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Congenital heart disease constitutes between 1% and 2% of all organic heart disease so that it is a rare finding in pregnant women. Abbott's grouping[1] of these cases according to their tendency to cyanosis is of great importance because it affords a basis for predicting certain physiologic reactions under strain. This is particularly important when one wishes to arrive at a prognosis as to the effects of pregnancy and labor. Abbott's three groups are as follows: 1, the acyanotic group, those without abnormal communications between the right and left side of the heart; 2, the *cyanose tardive* group, those with an arteriovenous connection with the possibility of transient or terminal flow from the venous to the arterial side; 3, the *Morbus Cæruleus* group with a permanent veno-arterial shunting of the blood. Diagnosis of the particular lesion present is notoriously difficult but the recent advances in diagnosis by means of Roentgen rays and the determination of the circulation rate from vein to lungs and from vein to periphery should be of definite assistance.

In 1905 Pouliot[20] stated that marriage was contraindicated in congenital heart disease only in the presence of cyanosis, and in 1912 Couderc[6] concluded that if the condition was compatible with adult life, the prognosis depended less upon the form of the lesion than upon the state of compensation, degree of cyanosis and polycythemia, parity, and advent of complications especially tuberculosis and endocarditis. In 1920 Hochsinger[10] emphasized the importance of preëxisting or developing cyanosis as an indication for the interruption of pregnancy, but more recently Shapiro and Simons[24] have stated that congenital heart disease even though accompanied by a high grade of cyanosis is not in itself a contraindication to pregnancy. Breed and White[3] state, "If a patient with congenital heart disease has survived to the childbearing age without signs of incapacity for normal activity she will certainly be able to pass through pregnancy and labor without difficulty." Carr and Hamilton[5] concluded that cases without communication between right and left sides of the heart or between the aorta and pulmonary artery did well, whereas those in which the possibility of veno-arterial shunt existed sometimes developed sudden alarming symptoms as a result of the pressure changes which follow sudden emptying of the uterus. These symptoms most commonly developed after Cesarean section or internal podalic version and in some instances death had followed. The authors advocated postpartum binding of the limbs and abdomen to increase and maintain peripheral resistance.

In view of the varying opinions expressed by these different authors, it seemed important again to review a group of patients with congenital heart disease since there have only been sporadic case reports since the series collected by Couderc in 1912. Since 1932 at the New York Lying-In Hospital there have been 1089 recognized cases of organic heart disease in approximately 31,000 obstetrical patients. Of these 1089 cases, 20 (1.89%) have been diagnosed as having congenital heart disease and are summarized in Table 1.

There were 8 cases diagnosed as pulmonic stenosis, their average age being 24 and the average parity 0.5. It is not without some hesitation that we present a clinical group with this as the primary diagnosis but it was the sole discharge diagnosis in each instance. The cases, however, presented a common clinical picture indicating a congenital lesion which differed from the other diagnostic groups. All had a loud systolic murmur and most of them a thrill over the pulmonic area. There were varying degrees of enlargement of the heart and of the pulmonary conus. It is probable that other lesions also were present and possibly the tetralogy of Fallot in most of them, with its association of pulmonic stenosis, dextroposition of the aorta, patent interventricular septum and right ventricular hypertrophy. This is particularly likely to be the case in the

TABLE 1.—DATA ON 20 PREGNANT WOMEN HAVING CONGENITAL HEART DISEASE.

| Case. | Diagnosis and functional class. | Age. | Parity. | Gravidity. | Cyanosis. | Electrocardiogram. | Roentgen ray and fluoroscopy of heart. | Duration of labor, hrs. | Blood loss, cc. | Comment. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. J.H. | Pulmonic stenosis Class 2 | 23 | 0 | 1 | 0 | RAD | Mod. enlargement, prominent pul. conus | 10 | 100 | Dysp. on exertion since infancy. Systolic thrill and murmur over pulmonic area. Mild clubbing. Nor. preg., labor, and puerperium. |
| 2. M.R. | Pulmonic stenosis Class 2 | 25 | 1 | 2 | Sl. | RAD | Markedly enlarged pul. conus. No gen. enlargement | (a) 36* (b) 21 | 100 500 | Dysp. on exertion since childhood. Syst. thrill and murmur over pul. area. No clubbing. Cyanosis and orthopnea in both preg. Labors nor. |
| 3. A.A. | Pulmonic stenosis Class 2 | 24 | 1 | 2 | 0 | Neg. | Sl. enlargement l. aur. large pul. conus | 24 | 140 | Dysp. on exertion since childhood. Syst. thrill and murmur over pul. area. No clubbing. Nor. preg., labor, and puerperium. |
| 4. M.S. | Pulmonic stenosis Class 2 | 32 | 1 | 4 | Sl. | RAD | Marked enlargement, prominent pul. conus | (a) 5 (d) 5 | 40 | Dysp. on exertion since childhood. Syst. thrill and murmur at pul. area. Syst. murmur at apex. No clubbing. Cyanosis during latter part of preg. Nor. labor and puerperium. |
| 5. V.P. | Pulmonic stenosis Class 1 | 19 | 1 | 4 | 0 | RAD | Sl. enlargement, prominent pul. conus | (a) 7 (d) 7 | 50 | No history of card. disease. Syst. thrill and murmur over pul. area. No clubbing. Nor. preg., labor, and puerperium. |
| 6. M.P. | Pulmonic stenosis Class 2 | 25 | 0 | 1 | Sl. | RAD | Mod. enlargement, prominent pul. conus | 4 | 70 | Known heart dis. since childhood with dysp. on exertion. Syst. thrill and murmur over pul. area. Clubbing present. Cyanosis, orthopnea, and palpitation during latter part of preg. Nor. labor and puerperium. |
| 7. E.J. | Pulmonic stenosis Class 2 | 22 | 0 | 1 | 0 | Neg. | Prominent pul. conus; nor. sized heart | ... | ... | Known heart dis. since birth. Severe hypert. since 15 and one episode of renal failure at 21. Syst. murmur and inconstant thrill at pul. area. Edema of eye grounds. No clubbing. Therap. abortion at 3 mos. |
| 8. D.T. | Pulmonic stenosis Class 3 | 22 | 0 | 2 | Mod. | RAD | Marked enlargement; prominent pul. conus | .... | ... | Known heart dis. since birth with cyanosis and dysp. on exertion. Syst. thrill and murmur at pul. area. Syst. murmur at apex. No clubbing. Preg. at 19: therap. abortion 3 mos. Preg. at 22. Episode of card. failure at 5 mos. assoc. with pneumonia. Spontaneous labor, low forceps delivery at term. |
| 9. C.S. | Interventricular septal defect Class 3 | 30 | 2 | 4 | 0 | LAD | Mod. enlargement | 6 | 50 | Dysp. on exertion since childhood. Syst. thrill and murmur 3d and 4th interspace to left of sternum. No clubbing. Dysp., orthopnea, and palpitation latter part preg. Labor and puerperium nor. |
| 10. A.S. | Interventricular septal defect | 28 | 2 | 4 | 0 | LAD | Sl. enlargement | (a) 8 (b) 5 | 200 | Known heart dis. and dysp. since childhood. Syst. apical thrill and murmur. No clubbing. Nor. preg., labor, and puerperium. |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 10. A.S. | Interventricular septal defect Class 2 | 28 | 2 | 4 | 0 | LAD | Sl. enlargement | (a) 8<br>(b) 5<br>(d) 23 | 200 | Known heart dis. and dysp. since childhood. Syst. apical thrill and murmur. No clubbing. Nor. preg., labor, and puerperium |
| 11. P.P. | Interventricular septal defect Class 2 | 26 | 0 | 1 | 0 | Neg. | ..... | 11 | 50 | Known heart dis. since childhood. Syst. apical thrill and murmur. Mild clubbing. Nor. preg., labor, and puerperium. |
| 12. C.G. | Interventricular septal defect Class 1 | 29 | 1 | 3 | 0 | Neg. | Mod. enlargement | (a) 2<br>(b) 24 | 100 | No known hist. of heart dis. Apical syst. thrill and murmur. No clubbing. Nor. preg., labor, and puerperium. |
| 13. R.P. | Coarctation of the aorta Class 3 | 26 | 0 | 1 | Sl. | LAD | Mod. enlargement, notching of ribs absent aortic knob | ... | ... | Dysp. and palpitation for 6 yrs. Collat. circulation present. Apical and basal syst. murmurs. Feeble peripheral pulsations. Bl. press. RA 140/74. LA 130/80 not obtainable in lower extremities. Abnor. incr. in card. output. Elective Cesarean sect. at term. Normal puerperium. |
| 14. E.B. | Coarctation of the aorta Class 3 | 23 | 0 | 1 | Sl. | LAD | Sl. enlargement; no notching of ribs; small aortic knob | 4 | 20 | Known heart dis. since childhood with dysp. on exertion. No evidence of collat. circ. Syst. murmur over entire precordium trans. down aorta. Syst. thrill at base. Bl. press. RA 135/80, LA 130/60, RL 110/80, LL 100/80. Increased dysp. during preg., nor. labor, undue weakness during puerperium and develop. of diastolic murmur at base. Gen. cond. worse. |
| 15. R.Z. | Coarctation of the aorta Class 1 | 27 | 0 | 1 | 0 | LAD | Mod. enlargement; notching of ribs | ... | ... | Past hist. entirely neg. Collat. circulation present. Syst. murmur over entire precordium trans. down aorta. Bl. press. RA 200/100, LA 230/110, RL 125/110, LL 125/110. First seen at 4th mo. of preg. Cesarean sect. and tubal sterilization at term after prelim. digital. Course satisfactory. |
| 16. A.S. | Patent ductus arteriosus Class 1 | 21 | 0 | 1 | 0 | LAD | Mod. enlargement | 7 | 20 | No past hist. of card. dis. To and fro basal murmur. No clubbing. Nor. preg., labor, and puerperium. |
| 17. H.G. | Patent ductus arteriosus Class 2 | 26 | 1 | 2 | 0 | LAD | Mod. enlargement | (a) 22<br>(b) 8 | 80<br>50 | Dysp. on exertion since childhood. Syst. thrill and to and fro murmur at base. No clubbing. No difficulty during either preg., labor, or puerperium. |
| 18. G.B. | Patent foramen ovale Class 1 | 35 | 3 | 5 | 0 | LAD | Sl. enlargement | (b) 48<br>(c) 24<br>(d) 18<br>(e) 16 | <br><br><br>80 | Known heart dis. since childhood. Loud syst. murmur 3d left interspace. No clubbing. No difficulty during pregnancies, labors, or puerperia. |
| 19. M.M. | Congenital defect unclassified Class 1 | 25 | 0 | 2 | 0 | LAD | Mod. enlargement | 50 | 250 | Known heart dis. since childhood. Loud syst. murmur 4th left interspace. Slight clubbing. No difficulty during preg., labor, or puerperium. |
| 20. L.W. | Congenital defect unclassified Class 1 | 20 | 0 | 1 | 0 | Neg. | ..... | ... | ... | Spontaneous abortion at 18 wks. Past hist. neg. except for known murmur since childhood. Loud syst. murmur over entire precordium. No clubbing. |

* Letters refer to pregnancy for which information was available.

4 patients with cyanosis. As the authors had not personally seen all these patients it seemed better to treat them as a group in spite of the fact that some were more definitely suggestive of the tetralogy than others. Another reason for this decision is the frequency of the diagnosis of pulmonic stenosis in reports in the obstetrical literature so that this group is comparable with these cases.

Therapeutic abortion was performed in 2 instances. The first patient, Case 7, was a 22-year-old white primigravida with known congenital heart disease since birth. At the age of 15 she developed severe hypertension which was associated with headaches, dizziness, and marked dyspnea on exertion. At 21 she had an episode of renal failure. When first seen in the early part of pregnancy there was bilateral retinal edema. Cardiac examination revealed a loud systolic murmur and an inconstant thrill over the pulmonic area. Cyanosis and clubbing were absent. Blood pressure was 210/130. A roentgenogram of the chest revealed an enlarged pulmonary conus without appreciable cardiac enlargement. The electrocardiogram was negative. The vital capacity was 2000 cc. Blood chemistry and renal function tests were normal. Therapeutic abortion was performed under local anesthesia at 3 months' gestation primarily because of the hypertension and the past history of renal failure.

The second patient, Case 8, colored, aged 19 years, was also known to have had congenital heart disease since the time of birth, cyanosis and marked dyspnea on exertion having been present frequently. There was marked cardiac enlargement, a systolic murmur and thrill at the pulmonic area, and a systolic murmur at the apex. There were no pulmonary râles, edema or liver enlargement. The vital capacity was 1500 cc. Clubbing and polycythemia were absent. The electrocardiogram revealed right axis deviation. Cardiac films revealed enlargement of all chambers and fullness of the pulmonary conus. Because of the marked cardiac enlargement and the low cardiac reserve a therapeutic abortion was performed under open drop ether at 3 months' gestation. The patient was discharged in a satisfactory condition. She was seen again 3 years later when she appeared at the clinic 5 months pregnant suffering from lobar pneumonia and mild cardiac failure. She was digitalized and received 44 gm. of sulfathiazole over a period of 8 days. She recovered from the pneumonia. At this time Roentgen ray study, electrocardiograms and clinical examination failed to reveal any significant changes since the previous admission. In view of the advanced stage of the pregnancy the patient was kept on restricted activity in the hospital under digitalis therapy until delivery. She went into spontaneous labor at term and was delivered by low forceps at full cervical dilatation under local anesthesia. Throughout labor the pulse and respirations did not rise significantly, the maximum pulse rate being 96 and the maximum respiratory rate 22. The postpartum course was uneventful.

In this group of patients cardiac enlargement was present in 6. Mild cyanosis was present in 4 cases without increased intensity being noted during pregnancy or labor, and none had polycythemia. Three patients (Cases 2, 6 and 8) of the 4 who were cyanotic, complained of dyspnea on exertion which began about the fourth month of gestation, increased as pregnancy progressed but never became more than moderate in degree. The Functional Capacity (according to the scheme of the New York Heart Association) was diagnosed Class 2 in 2 cases, Class 3 in the other. Neither in these 3 cases nor in any other of the pulmonic stenosis group did the respirations rise above 24 per minute during labor. The fourth cyanotic patient suffered from dyspnea and palpitation throughout pregnancy with relief shortly after delivery. Neither this patient nor any other of the pulmonic stenosis group had a pulse rise over 110 per minute during pregnancy or labor. To summarize then, except for the 2 cases which required therapeutic abortion and the 1 patient who was successfully treated for pneumonia, this group presented no serious problems during pregnancy, labor or the puerperium.

Including the series of Couderc,[6] Naish,[16] and Jensen[11] there are 25 other reported cases of pulmonic stenosis complicating pregnancy. Jensen found the average age to be 22.9 and the average parity 1.5. There are no deaths which could be attributed to the lesion. Three patients had symptoms of cardiac insufficiency during pregnancy (Durozier,[8] Laënnec,[13] and Sireday,[25] the last case being complicated by patent foramen ovale), 2 patients had cardiac difficulty during labor (Courdec, Case 7, and Payraud,[17] the latter case being complicated by an interventricular septal defect).

In the present series there were 4 cases of interventricular septal defect the average age being 28 and the average parity 1.3. None had cyanosis or polycythemia. Three had cardiac enlargement and 1 complained of dyspnea and palpitation on exertion beginning about the fourth month of gestation, increasing as pregnancy progressed so that she was diagnosed as Class 3 Functional Capacity. There was some relief of the dyspnea at term prior to labor. In this case labor was uneventful, the pulse and respirations remaining at physiologic levels, and all symptoms disappeared within the first 24 hours postpartum. In summary, this group presented no serious problems during pregnancy, labor, or the puerperium.

Including the series of Couderc and Jensen there are 32 other reported cases of interventricular septal defect complicating pregnancy. Jensen found the average age to be 28.5 and the average parity 2.2. Two of the 4 recorded deaths can be attributed to the lesion—both died of congestive failure at 6 months' gestation (Ferraro,[9] and Jönen,[12] the latter case being complicated by a widely patent foramen ovale). Two patients had less serious cardiac difficulty during pregnancy (Bernard,[2] and Delsudre[7]), but there is no mention of difficulty during labor or the puerperium.

In the present series there were 3 cases of coarctation of the aorta all pregnant for the first time, the average age being 25. These cases have been previously reported in detail by Mendelson[15] together with a survey of the literature and analysis of the previously reported cases. All had cardiac enlargement and mild cyanosis with slight increase in hue as pregnancy progressed but never intense or accompanied by polycythemia. None had tachycardia during pregnancy but all experienced dyspnea beginning about the fourth month of pregnancy, increasing with the progress of gestation except for slight but definite relief prior to labor at term. The first patient was delivered by elective Cesarean section at term, the dyspnea disappeared within the first 24 hours postpartum, and the subsequent course was satisfactory. The second patient delivered spontaneously after a 4-hour labor during which the pulse and respirations remained at physiologic levels but postpartum the dyspnea became more severe and the general condition markedly worse. Definite cardiac and vascular changes were indicated by the development of a diastolic murmur to the left of the sternum. Cesarean section and tubal sterilization were performed in the third patient shortly after the onset of labor at which time the pulse rate had risen to 120 per minute and the respiratory rate to 30 per minute. Digitalis had been administered prior to operation and was continued for the first 2 days postpartum. The pulse and respiratory rates returned to normal within the first 48 hours and the subsequent course was satisfactory.

Mendelson found 29 other reported cases of coarctation of the aorta complicating pregnancy. The average age was 34 and the average parity 3. There were 5 deaths attributable to the lesion—2 from rupture of the aorta, 1 from cerebral accident, 1 from cardiac failure, and 1 from endocarditis, and in over one-half the cases pregnancy and labor had a deleterious effect upon the patient's condition. With these patients a satisfactory clinical condition does not necessarily indicate a good immediate prognosis for there are the ever-present dangers of aortic rupture, cerebral accident, or valvular damage, and these risks are enhanced by the physiologic mechanisms of pregnancy and labor.

In the present series there were 2 cases of patent ductus arteriosus, the average age being 24 and the average parity 0.5. There was no instance of dyspnea, cyanosis, polycythemia, or any cardiac difficulty during pregnancy, labor, or the puerperium.

Including the series of Couderc and Jensen there are 31 other reported cases of patent ductus arteriosus complicating pregnancy. Jensen found the average age to be 27.2 and the average parity 2.2. There are 6 recorded deaths only 2 of which can be attributed to the lesion—1 died of congestive failure at 5 months' gestation (Schulcz[23]) and the other died of congestive failure following Cesarean section

at term (Tunis[26]). There is no mention of any cardiac difficulty during pregnancy, labor, or the puerperium, in the other cases.

In the present series there was 1 case of patent foramen ovale—a 35-year-old para III gravida V who was free of dyspnea, cyanosis, polycythemia, or difficulty during pregnancy, labor, or the puerperium.

Including the series of Couderc and Jensen there are 18 other reported cases of patent foramen ovale complicating pregnancy. Jensen found the average age to be 32.5 and the average parity 6.6. There are 10 recorded deaths only 6 of which can be attributed to the lesion (Campbell,[4] Jönen,[12] Porak,[19] Rudaux,[22] Perreymond,[18] and Rosemund[21]—the last 2 cases being complicated by other medical conditions). Therapeutic abortion was performed in 1 case which survived (Löwi[14]). In the remaining 7 cases there is no mention of any cardiac difficulty during pregnancy, labor or the puerperium.

In the present series there were 2 cases without a specific diagnosis of the congenital anomaly. In neither was there dyspnea, cyanosis, polycythemia or other cardiac difficulty. The one had a normal delivery and the other a spontaneous abortion at 18 weeks.

Although not encountered in this series, mention is made for the sake of completeness of two other rare congenital defects—dextrocardia and congenital hypoplasia of the aorta. Dextrocardia *per se* does not constitute a problem, although the anomaly is frequently associated with other defects. Jensen found 5 cases of isolated dextrocardia in which pregnancy was entirely uneventful. Congenital hypoplasia of the aorta is usually associated with sexual immaturity and is rarely seen in childbearing women. There are in the literature 2 deaths during pregnancy attributed to this lesion, both due to cardiac failure—1 at term (Weibel[28]), and the other postpartum (Wagner[27]), but no other complications are recorded.

The cardiac Functional Capacity of the patients in the present series according to the scheme of the New York Heart Association is seen in Table 2.

Patients with cardiac disease are placed in Class 1 when there is no limitation of their physical activity because of the heart; Class 2 patients show slight limitation of their physical activity by symptoms due to the heart; Class 3 patients show marked limitation by such symptoms on attempting physical activity, while Class 4 patients have such symptoms while at rest and any physical activity will increase these symptoms.

TABLE 2.—RELATION OF PARITY AND CARDIAC FUNCTIONAL CAPACITY.

| | Class 1. | Class 2. | Class 3. | Class 4. |
|---|---|---|---|---|
| Total number of patients | 7 | 9 | 3 | 1 |
| Primigravidæ | 4 | 4 | 3 | 0 |
| Multigravidæ | 3 | 5 | 0 | 1 |

It will be noted that 80% of the patients were in Classes 1 or 2. Except for the 1 case of cardiac failure (Case 8) there was no change in the functional capacity during pregnancy, labor, or the puerperium. Classes 2 and 3 patients were admitted for rest, observation, and evaluation at least 2 weeks before term. An increase in parity did not seem to be associated with a more serious cardiac situation, the one case subjected to therapeutic abortion because of heart disease being a primigravida with pulmonic stenosis and marked cardiac enlargement and this patient was successfully delivered at term in a subsequent pregnancy.

It has been customary to administer digitalis to patients in Classes 2 and 3 if the pulse or respirations exceed physiologic levels early in labor prior to the onset of bearing down efforts, as it is believed that impending cardiac failure may be averted or more rapidly and efficiently treated by such procedure. In such patients also the second stage of labor would be eliminated or appropriately shortened by forceps delivery. In the present series digitalization was required in only 2 patients. In 1 of these Cesarean section was performed because of coarctation of the aorta, and in the other there was a complicating lobar pneumonia.

No signs or symptoms of veno-arterial shunt occurred in the group with lesions allowing for such an occurrence although there was no instance of major operative procedure, prolonged second stage, or excessive blood loss among those patients. Prolonged second stage is considered dangerous in this respect because of the possibility of unduly increased pressure in the pulmonary circuit from prolonged and excessive bearing down efforts. The judicious use of outlet forceps should help to reduce the chances of shunt due to these pressure changes. Careful observation during the first 24 hours postpartum failed to reveal any untoward symptoms or physical signs suggesting cardiac embarrassment.

There was no instance of intrapartum or puerperal infection. Congenital cardiovascular defects from a locus minoris resistentiæ and with this in mind strict attention is paid to aseptic technique, so that all procedures which increase the likelihood of infection are avoided if possible. Vaginal examinations are omitted, rectal examinations reduced to a minimum, and local anesthesia employed at delivery to guard against third stage hemorrhage. The average third stage blood loss for the series was 167 cc. whereas that for the average clinic patients is 247 cc.

**Summary and Conclusions.** The majority of patients with serious congenital heart disease succumb before reaching puberty. Those that survive require evaluation if childbearing is contemplated. In addition to the general physical condition, such factors as cardiac functional capacity, the size of the heart, the degree of cyanosis and polycythemia, and the particular lesion merit special consideration. Cyanosis *per se* is not a contraindication to pregnancy.

Pregnancy and labor present such definite risks to patients with coarctation of the aorta that contraception should be practised in this condition. If discovered early in pregnancy therapeutic abortion is indicated, but if gestation is far advanced and interruption from below not feasible, delivery should be effected by Cesarean section and tubal sterilization performed.

Cases of widely patent foramen ovale, interventricular septal defect, and patent ductus arteriosus form another special category by virtue of the possibility of veno-arterial shunt. Such an occurrence has not been observed in this series but certain precautions should be taken to avoid the possibility of the rare but serious accidents referred to in the literature. Arterial blood pressure should be maintained by avoiding traumatic procedures and postpartum hemorrhage, or by promptly instituting appropriate therapeutic measures in the event of such occurrences. Local anesthesia at delivery will decrease third stage blood loss and the judicious use of outlet forceps will obviate undue bearing down efforts with resulting increased pressure in the pulmonary circuit. Particular attention should be paid to the avoidance of infection.

Classes 2 and 3 patients should be admitted several weeks prior to term for rest and study. In such patients with cardiac enlargement digitalis should be used if the pulse or respiratory rate exceeds physiologic levels early in labor, before the onset of bearing down efforts. The second stage of labor should be eliminated for these patients or appropriately shortened by forceps delivery. Careful observation should extend throughout the first 24 hours postpartum.

The difference between the lack of mortality in this series and the 11% mortality reported in the 135 cases from the literature is surprising. We encountered only 1 patient in Functional Class 4 and 3 patients in Class 3. If 2 or 3 of these had died there would have been a mortality in our series comparable to the figures in the literature. We realize that there is a tendency for the literature to contain the most severe cases and particularly cases that have died, because these are likely to afford a more exact diagnosis through the possibility of an autopsy being performed. We would like to think that our low mortality is in part at least due to the care with which our patients have been followed and particularly to the attempts which were made by using rest and digitalis and appropriate obstetrical procedures to save those patients with any signs of cardiac insufficiency from encountering a strain during pregnancy or labor which might have been harmful.

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## PREGNANCY AND THE DEVELOPMENT OF MAMMARY CANCER.*

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The 2 clinical cases that we report below and the facts that became apparent in the course of this study suggest a certain number of reflections. We shall begin by describing the evolution of the process in the 2 cases and then present the connections that we feel justified in making.

**Case Reports.** Case 1.—Madam S, aged 35, had been treated up to 1937 for a calculous cholecystitis with several crises of hepatic colic. In 1937, following a double postpartum phlebitis, which required 2 months in bed, this patient noticed several lumps in the upper part of her right breast. She consulted a number of physicians and surgeons all of whom agreed in the diagnosis of benign adenomata. This was confirmed by histologic examination of a nodule removed at biopsy. Up to 1939 the patient remained in excellent health, continuing her daily work. The breast nodules, examined on several occasions, showed nothing suspicious. There was no adenopathy or evidence of malignant change, but rather a progressive diminution in size.

The patient went through a normal pregnancy beginning in June, 1938. She was delivered of a normal infant at term, and had a normal lactation period. But 10 days after her delivery, before leaving the hospital, there was noticed in the upper part of the greatly enlarged lactating breast, at the level of the biopsy scar, an induration about half the size of a hen's egg. This induration had not been present on the day of her delivery. This

* Difficulties of transatlantic correspondence have prevented the author from correcting the proof of this article. It has also been impossible to secure from him illustrations or a completed list of references.

mass, opaque to transillumination, made us fear a carcinoma of the breast. There was already in the axilla a small but hard and mobile lymph node. This, with the reservations necessary for the frequency of errors in clinical diagnosis in this field, appeared to have neoplastic characteristics in spite of the rapidity of its appearance.

There was nothing abnormal in the supraclavicular region; radiologic examination of the thorax showed no change that could be interpreted as neoplastic. The laboratory reported nothing abnormal except a marked increase of the blood cholesterol.

Our advice to the family was as follows: in view of the patient's postpartum asthenia, to commence radiotherapy of the neoplastic region and of its proximal vascular zone, to be followed later by a surgical excision of the mammary and maxillary region. To our great regret, the patient refused radiotherapy because her mother-in-law had died following Roentgen ray therapy. We therefore with the patient's approval decided on surgical operation. This was carried out without incident, according to Halsted's method, and the material referred to M. Peyron, of the Pasteur Institute, for pathologic study. *Microscopically*, the large mammary gland was covered at the level of the neoplasm by a thickened skin that looked like the skin of an orange. The gland was heavy and in a number of areas round nodules were palpable that suggested adenoma. On section, an epithelial tumor was found, hard, not circumscribed, and presenting a white gelatinous appearance. Histologic examination of a number of sections from different parts of the mass revealed a glandular carcinoma with large cells occurring in a loose connective tissue framework. The neoplastic cells were markedly pleomorphic, mostly large and either rounded or elongated with irregular outlines. The protoplasm was clear with an irregular, often fragmented nucleus and other signs of degeneration. The frequent mitoses were atypical, sometimes multipolar. The acini were atrophic, the ducts dilated and contained more or less necrotic débris. The lymph nodes were congested with capillary dilatation. There was marked histiocytic reaction in the connective tissue. No neoplastic cells were found anywhere. The nodules scattered through the mammary gland proved microscopically to be cystadenomata without malignant degeneration.

Case 2.—A woman, aged 40, had no relevant family history; had had lobar pneumonia at 25 years of age, a mammary abscess after her first pregnancy at 28 years, and suffered since youth from a chronic gastritis. At the age of 10 she had had an adenoma of the breast removed. Numerous microscopic examinations confirmed the benign adenomatous nature of this tumor. In addition, her general condition and the clinical aspect of the tumor gave no doubt as to its benignancy.

At 35 the patient again became pregnant without postpartum complications or aggravation of the tissues formerly operated upon. In January, 1939, at the age of 40 and when 8½ months pregnant, the patient noticed in the mammary scar a nodule which had not been there before. This did not have the typical clinical appearance of an epithelioma of the breast, but 10 days before delivery it rapidly increased in size. This induration became about the size of a hen's egg and showed the clinical signs of an epithelioma. There was also a hard and slightly movable adenopathy in the axilla. The operation took place under good circumstances. The tissue, studied grossly and microscopically, showed epithelial masses. The cells were very pleomorphic, mostly cuboid and cylindrical. There was a complete change in the architecture of the organ. Gigantic and mitotic cells were particularly numerous, showing the malignant nature of the tumor and explaining the invasion of the adjacent tissue and the malignant involvement of the axillary lymph nodes.

**Comment.** These clinical and pathologic data in our 2 patients made it desirable to consider the biologic problem of the relation between pregnancy and the development of cancer. We shall not discuss all the opinions that have been given on this subject, but wish to emphasize in these 2 cases the brusque appearance during the preparatory stage of lactation, of epitheliomas in the old scars of adenomas; in other words, when physiologic factors were determining changes in the mammary tissue of a pregnant woman.

It is difficult to obtain a precise idea about the development of mammary cancer during pregnancy or after delivery. Certain authors maintain that pregnancy and the puerperium favor the development of mammary cancer, incriminating the follicular hyperplasia incident thereto. Others, however, preach the contrary. The statistics of human pathology, and clinical and laboratory research in experimental cancer of animals, have not only not given conclusive results, but have even been contradictory. In human pathology, Lacassagne, who was able to produce a mammary cancer in male mice by injections of folliculin, has shown that folliculin arrives in abundance in the human mammary gland while this organ is being congested with blood. The colostrum contains folliculin in considerable amount, at least equal to that found in the urine. It is therefore probable that the mammary congestion in the menstrual period is also accompanied by the passage of hormones into the mammary cells and mammary ducts where it may accumulate. All this tends to establish that some women may retain folliculin either in the mammary glands as a whole or in parts of them. As a result of the prolonged irritation of the epithelium of the ducts a hypersecretion is produced, then epithelial overgrowth, and finally a proliferation with infiltrating tendencies—carcinoma. Furthermore, Micale has shown that the puerperium favors the development of cancer and incriminates the hyperfolliculinism of pregnancy. The American authors, Goormaghtigh, Armerlink, and others who have published lengthy studies on this subject, arrive at the same conclusion, namely that in human pathology the hyperfolliculinism of pregnancy and the puerperium are carcinogenic factors.

Among those who preach the contrary views, let us cite Bentivoglio, who observed a case of leukemia that was improved after childbirth. Simonnet also does not believe in the production of cancer of the breast by hyperfolliculinism. This author however admits that folliculin can favor cellular development, but without tendency toward cancer. Thus in human pathology this problem has not given consistent results.

Let us pass now to the domain of experimental cancer. The principal authors who have studied the carcinogenic effect of pregnancy and puerperium in laboratory animals are Lacassagne,

Amandio Tavares, Loeb, Murray and Simonnet. Lacassagne has produced a mammary cancer in the male mouse by the injection of folliculin, and has studied the causes of the development of cancer in folliculinized mice as well as the varied action of folliculin in various strains of mice. It appears indisputable, he says, that the adenocarcinoma of mice is the result of a prolonged stimulus to proliferation that is exercised by folliculin on the cell of the mammary gland.

In the same way Amandio Tavares and Ernesto Morais have studied the influence of ovarian castration on the development of tar tumor in rabbits. In the first group both ears of 25 bilaterally castrated rabbits were painted from the 7th or 8th days after castration. The applications were made twice a week for 7 months. A second group of 25 rabbits were painted only, to serve as controls. In the 25 castrated rabbits 10 died from the 5th to 77th day after the application was begun without developing tumors. The first papilloma appeared on the 34th day, most of them developing before the 80th day. In this group 3 carcinomas developed, confirmed histologically on the 62d, 151st, and 206th day. In the controls 11 died without any neoplastic development between the 3d and 125th day. The first nodule appeared on the 18th day, and 5 cases of carcinoma were diagnosed by biopsy (21st, 64th, 69th, 155th and 158th days). Comparing the results of these two series, the authors note that the castrated rabbits withstood the tarring as well as the normals and that most of the nodules had accomplished their development in both groups before the 80th day.

Concerning the evolution of the tumors, there were noted in a period of 7 months histologically malignant neoplasms in 3 castrated females as opposed to 5 in the control rabbits. The development of cancer was not only a little more frequent but more precocious in the latter group, to which belonged the one example in these experiments of a precocious cancer (*i. e.*, diagnosed histologically before the 30th day). One may infer, then, that castration rendered the terrain less propitious to the development of tar cancer. These facts tend to confirm the inhibiting effect of castration and to suggest the influence of sexual hormones on the tumor development. The authors remark, however, that in these as in former experiments their observations show the importance of individual susceptibility in the pathogenesis of experimental cancer. The tumor nodules were not regularly either more numerous or larger in the normal rabbits than in those deprived of their sex glands. In both groups there were observed examples of rapid or slow growth, persistent or transient duration. Also, they obtained two excellent examples of ulcerating carcinoma in the castrated rabbits.

Loeb and Murray have produced adenocarcinoma of the breast in mice by the repeated injections of large doses of folliculin ben-

zoate. With smaller doses only doubtful results were obtained. These tumors were produced in strains of mice in which the males did not produce spontaneous cancer. The frequency of the lesions appears to be a function of the greater or lesser sensibility of the strains of mice to folliculin (Lacassagne). After a certain age the heredity factor appears not to play any part. Lacassagne, Goormaghtigh and Amerlink have given a detailed description of these lesions.

The cutaneous application of folliculin can also provoke a mammary carcinoma in the male mouse (Burrows). Schockaert also attributes the stimulating effect of pregnancy and delivery on the development of mammary cancer to the hyperfolliculinemia of pregnancy and the puerperium. The structural and functional changes that occur in the mammary gland during the sexual cycle have an interesting repercussion on the problem of mammary cancer.

It is especially Simonnet who combats these views concerning the experimental production of cancer by folliculin. In his thesis entitled "The Role of the Follicular Hormone in Normal and Pathological Physiology," he writes "How shall we interpret the role of folliculin in the development of tumors?" Folliculin, he says, can stimulate cell development, but has no influence on the speed of mitoses. It provokes them but does not hasten them. It can also in exaggerating a physiologic process favor the action of a carcinogenic agent, but it does not appear to be a carcinogenic agent itself. Other observations made by Babes and Buclear on this subject, which offer from a biologic point of view some advantages that will not be insisted upon here, have not produced concordant results. While Babes alludes to an ovarian hyperplasia in the tarred rabbits caused by a multiplication of interstitial cells, Buclear opposes this interpretation and regards the ovarian hyperplasia as connected with the estrus period during which the ovaries were removed.

American investigators who are in accord on the carcinogenic effect of folliculin have proposed castration or ovarian blockade by Roentgen ray of women who have carcinoma of the breast in order to prevent recurrences and metastases. Adair and Pack, who with many pathologists accept the rôle of milk stagnation in the production of mammary cancer in the family, have proposed the aspiration of the stagnant milk with an electric pump. Instead of this mechanical treatment, may one not look hopefully for a hormone antagonistic to folliculin, perhaps a galactogenic hormone which would permit an evacuation at will of the products cyclically accumulated in the mammary glands? We may mention also that the laboratory shows that hyperfolliculinism is almost constant in tumor patients: the blood of those who have malignant tumors

contains up to 9000 mouse units per liter, the urine up to 5000 mouse units per liter.

In the presence of such inconclusive and even controversial results, we may well ask what then was the factor other than folliculin, which made the malignant tumor appear in our 2 patients after delivery?

**Summary.** Our two observations concerned the clinical history of 2 multiparæ each of whom previously had had an adenoma of the breast removed and developed a carcinoma in the scar during a subsequent pregnancy. It is obvious that in these 2 cases there was a close connection between the preparation for lactation and the development of cancer in the previously adenomatous breast. Without discussing the pros and cons of the question of the influence of pregnancy and the puerperium on the genesis of cancer, we wish to emphasize the sudden appearance of a carcinoma in an old scar of an adenoma at a time when a physiologic manifestation of the mammary tissue was in progress. We are in accord with those cancer investigators who think that the hyperfolliculinism of pregnancy favors the development of mammary cancer. Should one attribute this to the prolonged irritation of the mammary epithelium by folliculin, or perhaps to the loss of equilibrium (neurovegetative, vascular, hormonal) that accompanies the change from the stable condition of the 9 months of pregnancy to the puerperal state, a change which is capable of provoking pathologic activity of a carcinogenic nature?

We believe also that the amount of folliculin plays its rôle in the genesis of cancer. We know that Roentgen rays in sufficient doses may kill the cancer cell, but in smaller doses may provoke cancer (the cancer of the radiologists). Colchicine stimulates or inhibits mitosis according to the dosage. The same variation might occur with folliculin. No doubt the therapeutic abuse of folliculin might in some cases favor the development of cancer. We may also hope for a hormonal antagonist to folliculin which would permit the evacuation or the destruction of harmful substances periodically emptied into the blood.

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# CONCENTRATED LIVER EXTRACT IN THE MAINTENANCE TREATMENT OF PERNICIOUS ANEMIA.

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During the last 2 or 3 years an effort has been made by a committee appointed for revision of the United States Pharmacopœia to rate the efficacy of various manufactured substitutes for whole liver. A great deal has appeared in the literature concerning the use of unconcentrated liver extract in large doses and there seems to be no question that the various preparations given in 10-cc. doses are effective. A number of reports from foreign countries have been studied in this respect. Most of these are concerned with the use of extract given in 5-cc. doses. Writers from foreign areas apparently consider this a concentrated form of extract. The preparation most widely used by these workers is "Campolon."* Thus Bell,[1] Hoff,[14] Meulengracht,[18a,b] Schittenhelm,[22] Schulter,[23] Wendt,[24] and others[11,13] have reported on the results obtained from doses of 5 cc. or more. In 1938 Murphy and Howard[20] reviewed 31 cases which they had treated with 1-cc. doses of Lederle's Concentrated Liver Extract. Their tables on their own results and on those of others are available for study. With the exception of Murphy and Howard's[20] and Hartfall's[12] series, no reports of cases treated with doses of less than 3 cc. are quoted by them.

This contribution deals mainly with maintenance of the patient with pernicious anemia in a state of well-being and good health particularly under treatment with "Reticulogen."† The clinical material used in the analysis is derived mainly from the hematology clinic of the New Haven Dispensary where we have treated 31 cases of proven pernicious anemia with Reticulogen. In addition, we have incorporated the results of 9 private cases. No attempt to select favorable cases has been made. All new cases coming to the dispensary during the past 3 years have been subjected to Reticulogen therapy unless there was some special reason for use of another preparation. In addition, a certain number of cases which had been treated by other means were transferred to Reticulogen. Some persons have been kept on other forms of therapy to serve as controls. As controls we have also individuals

* A Liver Extract, product of Winthrop and Company.
† Extremely Concentrated Liver Extract, product of Lilly and Company.

who were formerly on oral liver or less concentrated extracts* and who are now maintained on Reticulogen.

A considerable portion of the liver extract used in this study was contributed by the makers (Eli Lilly & Co.) and the patient was thereby relieved of approximately one-half of the expense of treatment over a 2-year trial period. In the tables "cost" is computed to include this item at ordinary hospital prices so that it refers to the amount which the patient would have had to pay under ordinary circumstances. What this group of patients actually paid is approximately one-half of this amount.

TABLE 1.—RESULTS OF 12 CASES TREATED WITH ORAL LIVER EXTRACTS.

| Case.† Name. | Age. | Sex. | Treatment (wks.). | Interval (wks.). | Preparation liver ext. | Aver. R.B.C. (millions per c.mm.). | Aver. Hb., %. | Cost per week. |
|---|---|---|---|---|---|---|---|---|
| 1. M. B. | 58 | F | 208 | Daily | Lextron | 2.7 | 75 | $3 |
| 2. E. B. | 53 | M | 180 | Daily | Squibb's | 5.0 | 97 | $2 |
| 3. I. B. | 60 | F | 104 | Daily | Lilly's | 4.5 | 99 | $3 |
| 4. | | | | | | | | |
| 5. | | | | | | | | |
| 6. | | | | | | | | |
| 7. B. F. | 48 | F | 72 | Daily | Squibb's | 3.6 | 78 | $3 |
| 8. | | | | | | | | |
| 9. | | | | | | | | |
| 10. H. H. | 55 | F | 156 | Daily | Squibb's | 3.9 | 80 | $4 |
| 11. R. H. | 48 | F | 130 | Daily | Squibb's | 3.6 | 81 | $4 |
| 12. | | | | | | | | |
| 13. | | | | | | | | |
| 14. D. McK. | 43 | F | 300 | Daily | Raw liver | 4.5 | 87 | ? |
| 15. | | | | | | | | |
| 16. | | | | | | | | |
| 17. | | | | | | | | |
| 18. | | | | | | | | |
| 19. | | | | | | | | |
| 20. F. N. | 65 | F | 104 | Daily | Squibb's | 4.0 | 87 | $4 |
| 21. | | | | | | | | |
| 22. | | | | | | | | |
| 23. G. P. | 49 | F | 170 | Daily | Squibb's | 3.9 | 80 | $4 |
| 24. H. P. | 67 | F | 60 | Daily | Squibb's | 3.7 | 80 | $4 |
| 25. | | | | | | | | |
| 26. | | | | | | | | |
| 27. L. M. S. | 65 | F | 130 | Daily | Squibb's | 4.0 | 84 | $4 |
| 28. M. S. | 46 | F | 130 | Daily | Squibb's | 3.5 | 78 | $4 |

Patients who had either chronic complicating disease or acute episodes were not excluded from this report and, in some instances, this fact accounts for results which are not completely satisfactory.

Two patients have been treated for only 2 years; the rest have all been treated for 3 or more years.

**Results.** The standards which we have applied as the measure of the success of treatment include: Red Blood Cell Counts; Hemoglobin Percentage; Improvement in Patients' General Symptoms; Return to or Continuance in Occupation; Neurologic Symptoms and

* Some of the less concentrated liver extracts are: Abbott's Liver Extract, Campolon, Lilly's Concentrated Liver Extract.

† Case numbers, which are not continuous here, refer to the cases in Table 3.

Signs; Ability to Combat Chronic Associated Disease; and Ability to Withstand Acute Intercurrent Infections.

*Red Blood Cell Counts and Hemoglobin Percentage.* Our results are not as spectacular in the maintenance of these levels as are those of Murphy and Howard, but they do compare favorably with the reports of others,[2,4,6,9a,b,10,11,15,16] with patients under the care of Reznikoff,[25] at New York Hospital and with counts of the man or woman in average health in New Haven. In this regard it must be remembered that we have not selected our cases and that our patients are drawn for the most part from the poorer strata of society.

TABLE 2.—RESULTS OF 12 CASES TREATED WITH LILLY'S CONCENTRATED LIVER EXTRACT.

| Case.* Name. | Age. | Sex. | Treatment (wks.). | Interval (wks.). | Units per dose. | Aver. R.B.C. (millions per c.mm.). | Aver. Hb., %. | Neurol. findings. | Cost per week. |
|---|---|---|---|---|---|---|---|---|---|
| 1. | | | | | | | | | |
| 2. E. B. | 61 | M | 75 | 2 | 20 | 4.5 | 90 | Sub. imp. | $.25 |
| 3. I. B. | 61 | F | 52 | 2 | 20 | 4.8 | 94 | ... | $.25 |
| 4. | | | | | | | | | |
| 5. D. F. | 41 | F | 30 | 2 | 20 | 4.0 | 88 | Sub. imp. | $.25 |
| 6. K. E. | 68 | F | 104 | 2 | 20 | 4.0 | 88 | ... | $.25 |
| 7. B. F. | 49 | F | 68 | 2 | 20 | 4.0 | 88 | ... | $.25 |
| 8. P. G. | 58 | M | 100 | 2 | 20 | 4.8 | 96 | Sub. imp. | $.25 |
| 9. | | | | | | | | | |
| 10. | | | | | | | | | |
| 11. R. H. | 46 | F | 130 | 2 | 20 | 4.7 | 94 | ... | $.25 |
| 12. B. K. | 40 | F | 150 | 2 | 20 | 4.6 | 88 | ... | $.25 |
| 13. | | | | | | | | | |
| 14. | | | | | | | | | |
| 15. | | | | | | | | | |
| 16. | | | | | | | | | |
| 17. | | | | | | | | | |
| 18. | | | | | | | | | |
| 19. | | | | | | | | | |
| 20. F. N. | 62 | F | 180 | 2 | 20 | 4.6 | 85 | ... | $.25 |
| 21. | | | | | | | | | |
| 22. | | | | | | | | | |
| 23. G. P. | 50 | F | 104 | 2 | 20 | 4.3 | 86 | Sub. imp. | $.25 |
| 24. | | | | | | | | | |
| 25. | | | | | | | | | |
| 26. | | | | | | | | | |
| 27. | | | | | | | | | |
| 28. M. S. | 47 | F | 104 | 2 | 20 | 4.2 | 84 | ... | $.25 |
| 29. M. Wa. | 70 | F | 64 | 2 | 20 | 4.5 | 97 | ... | $.25 |
| 30. | | | | | | | | | |

* Case numbers, which are not continuous here, refer to the cases in Table 3.

*General Symptoms.* Nearly all the patients have noted either maintenance of previous good health or actual improvement in sense of well-being. Most of our patients have either continued to work at gainful occupations or have been restored to usefulness. Six were not able to work at the onset of therapy and are still unable to do very much. Eight were unable to work when Reticulogen was

started but are now returned to full function. Nearly every patient has gained weight and strength.

*Neurologic Symptoms and Signs.* Under subjective improvement we include such symptoms as relief from numbness and tingling, improved sense of well being, increased capacity for work and increased certainty in walking.

During the years when oral whole liver or liver extract were used, notes on the neurologic findings were few and so we have not tabulated them in this study. When the period of parenteral therapy was reached notations as to neurologic state became more frequent but were not made in many cases. Of the 12 cases treated by 5-cc. doses of Lilly's Concentrated liver extract 4 were noted to have had improvement in symptoms. The other 8 patients were at least maintained in *statu quo* and may have actually improved subjectively although the notes are not full enough to say positively. During the years of treatment with Reticulogen particular attention was paid to subjective and objective improvement in the neurologic state. Thirty-two of the cases have given evidence of symptomatic improvement; 8 have shown no improvement, but of these 4 (Cases 6, 15, 23 and 30) complained of no neurologic symptoms at the onset of treatment and are therefore considered to have been protected from their development during treatment. Four cases have shown no improvement or have actually become worse. Case 19 was very irregular in attendance at the clinic. Case 31 was complicated by epilepsy with frequent and severe convulsions. Case 24 was a very frail woman with chronic (quiescent) tuberculosis who passed through an attack of Type III pneumonia before the treatment with sulfathiazole was known and recovered to her previous health level and who later weathered one gall bladder operation but succumbed to a second one for adhesions.

Evidence of objective improvement has been found in numerous instances and has been substantiated by the kind coöperation of the neurologic division of the dispensary.

*Gait.* Twenty-one patients have shown improvement in gait which has been very marked in certain instances. Thus Cases 18 and 38 were completely bedridden at the onset of treatment and were restored to complete function and maintained with full ability to walk.

*Vibratory Sense.* Eleven of our patients have retained the normal response to vibratory stimuli; 21 have actually regained some portion of it, where it was absent when therapy was commenced.

*Reflexes.* Thirteen patients with relatively normal reflexes have been maintained in that state during treatment; in 17, improvement has been noted in this particular respect in those cases where reflexes were absent at onset of therapy.

*Sphincter Control.* During Reticulogen therapy 3 of our patients have regained a considerable amount of urinary sphincter control.

*Mental Symptoms.* In many instances memory has improved remarkably. Most of the persons under treatment have shown release from an unfriendly and suspicious attitude toward physicians and nurses. Patients who were uncoöperative at the start have become very helpful and trusting. Practically all who have had treatment for 6 months or more have no desire to stop because they appreciate so well the value they have received from it.

*Complication by Chronic Disease.* Sixteen patients have arteriosclerosis sufficiently advanced to be evident clinically. Four have arteriosclerotic heart disease. One has lived through two cerebral hemorrhages. Three have chronic gall bladder disease and have survived several acute attacks. One has developed signs of cirrhosis of the liver and has suffered a fracture of the surgical neck of the femur. Two have myxedema and 2 have thyrotoxicosis (1 of these had a thyroidectomy during the course of our therapy). Two have quiescent tuberculosis and 1 has developed acute exacerbations of tuberculosis without disturbing very much the blood picture. One has frequent and severe seizures of epilepsy and is being treated with dilantin. Three have syphilis—are under the usual forms of therapy, and 3 have chronic infectious arthritis.

*Complications by Acute Disease.* Nearly all have had mild upper respiratory disease on 1 or more occasions. Fifteen have had severe respiratory disease usually diagnosed as "grippe" or "influenza." Three have survived pneumonia. One has been successfully carried through 2 pregnancies. One had no major change in her blood status when thyroidectomy was performed.

It has seemed to us that these individuals, in spite of their pernicious anemia, have carried on about as well under these vicissitudes as does the average man under the same circumstances.

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FOOTNOTE FOR TABLE 3.

Of these 40 cases, 12 had previously been treated for long periods with oral liver preparations (Table 1), and 12 with Lilly's Liver Extract (Table 2).

"Interval (weeks)" = number of weeks between treatments.

"Aver. R.B.C." and "Aver. Hg." = average level of maintenance of these factors.

"Hemat." = hematocrit reading; "M.C.V." = mean corpuscular volume; "M.C.H." = mean corpuscular hemoglobin; "M.C.H.C." = mean corpuscular hemoglobin %. These factors were determined at various times during the course of the disease, the high levels of M.C.V. being in those instances where the tests were done at or near the beginning of treatment (Cases 1, 8, 28). The rest were completed after maintenance was considered to have been attained.

"Sub. imp." = subjective improvement.

"Gait, First and Last" refers to state at first and last examination of patient. "Imp." stands for improvement.

"Vibratory sense" and "Reflexes" also contain two lists under the headings of "First and Last." In these columns "Abs." refers to absence of the reflexes or vibratory sense; "Dim." to diminished and "Imp." to improved.

"Nor." refers to cases where the signs were not present at onset and did not develop during treatment.

The same terms and meanings are used in other tables.

* Private cases.

TABLE 3.—RESULTS OF 40 CASES TREATED WITH RETICULOGEN.

| Case. Name. | Age. | Sex. | Treatment (weeks.) | Interval (weeks). | Units per dose. | Aver. R.B.C. mills. per c.mm.). | Aver. hg. (%). | Hemat. | M.C.V. | M.C.H. | M.C.H.C. | Neurologic findings during treatment with reticulogen. | | | | | | | | Cost per week (dollars). | Complications. | End-results. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | Sub. imp. | Gait. | | Vibratory sense. | | Reflexes. | | Mental. | | | |
| | | | | | | | | | | | | | First. | Last. | First. | Last. | Fi t | Last | | | | |
| 1. M.B. | 62 | F | 130 | 3 | 20 | 4.7 | 88 | .. | 135 | 44 | 32 | Yes | Poor | Imp. | Abs. | Imp. | Dim. | Imp. | Nor. | .25 | Art. scler. | Health maintained; working. |
| 2. E.B.* | 61 | M | 208 | 4 | 20 | 5.0 | 90 | .. | .. | .. | .. | Yes | .. | .. | Abs. | Abs. | Abs. | Abs. | Nor. | .20 | Art. scler.; cor. hem. | Blood status good; not working. |
| 3. I.B. | 62 | F | 118 | 3 | 20 | 4.8 | 94 | 47 | 90 | 28 | 31 | Yes | Poor | Imp. | Abs. | Imp. | Dim. | Imp. | Imp. | .30 | Art. scler. | Health good; working. |
| 4. G.C. | 62 | F | 117 | 4 | 20 | 4.9 | 94 | 46 | 92 | 31 | 34 | Yes | Poor | Imp. | Dim. | Imp. | Dim. | | Nor. | .20 | None | Health good; working. |
| 5. R.dP. | 42 | F | 102 | 3 | 20 | 4.5 | 88 | 42 | 97 | 33 | 33 | Yes | N | or. | N | or. | Dim. | Imp. | Nor. | .30 | None | Health good; working. |
| 6. K.E. | 72 | F | 97 | 3 | 20 | 4.2 | 84 | 42 | 97 | 34 | 35 | Nor. | N | or. | N | or. | N | or. | Nor. | .25 | Art. scler.; grippe | Health good; working. |
| 7. B.F. | 50 | F | 107 | 2 | 20 | 4.3 | 88 | 42 | 102 | 33 | 32 | Yes | N | or. | N | or. | N | or. | Nor. | .25 | None; chr. bronchopneu. | Health good; working. |
| 8. P.G. | 62 | M | 128 | 3 | 20 | 4.8 | 88 | 45 | 107 | 33 | 32 | Yes | Poor | Imp. | Abs. | Imp. | Dim. | Imp. | Nor. | .25 | Chr. inf. arthritis; bronchopneu. | Health good; working. |
| 9. C.H. | 53 | M | 90 | 4 | 20 | 4.4 | 88 | .. | .. | .. | .. | Yes | Poor | Poor | Abs. | Abs. | Dim. | Dim. | Same | .20 | Psychiatric breakdown | Not known; working when last known. |
| 10. H.H. | 58 | F | 152 | 2 | 10 | 4.5 | 88 | 39 | 98 | 34 | 35 | Yes | N | or | Dim. | Imp. | Dim. | Imp. | Nor. | .10 | Cat. jaundice; chr. gall bl. | Health good; working. |
| 11. R.H. | 51 | F | 122 | 4 | 10 | 4.9 | 90 | 45 | 107 | 34 | 32 | Yes | N | or. | N | or. | N | or. | Imp. | .10 | Thyrotoxicosis; card. dis. | Blood status good; not working. |
| 12. B.K. | 43 | F | 122 | 2 | 20 | 4.5 | 86 | 42 | 100 | 33 | 33 | Yes | Poor | Imp. | Dim. | Imp. | Abs. | Abs. | Nor. | .40 | None | Blood status good; working. |
| 13. F.K. | 69 | F | 152 | 3 | 20 | 4.8 | 94 | 43 | 95 | 31 | 32 | Yes | Poor | Imp. | Abs. | Imp. | Dim. | Imp. | Nor. | .30 | Art. scler.; grippe | Health good; working. |
| 14. D.McK. | 49 | F | 110 | 4 | 20 | 4.4 | 88 | .. | .. | .. | .. | Yes | Poor | Imp. | Dim. | Imp. | Abs. | Imp. | Nor. | .20 | None | Health good; working. |
| 15. F.McL. | 35 | M | 80 | 3 | 10 | 4.8 | 97 | .. | .. | .. | .. | Nor. | Poor | Imp. | Dim. | Imp. | Dim. | Imp. | Nor. | .15 | Sensitive to Lederle's | Health good; working part time. |
| 16. R.McQ. | 69 | F | 118 | 3 | 20 | 4.7 | 94 | 45 | 95 | 30 | 31 | Yes | Poor | Imp. | Abs. | Abs. | Dim. | Dim. | Nor. | .30 | Art. scler.; grippe | Health good; working. |
| 17. M.M. | 74 | F | 123 | 4 | 20 | 4.3 | 86 | 43 | 100 | 30 | 30 | Yes | Poor | Imp. | Abs. | Imp. | Abs. | Imp. | Imp. | .20 | Art. scler.; grippe | Health good; working. |
| 18. M.Mi.* | 51 | F | 144 | 3 | 10 | 5.0 | 98 | 45 | 95 | 30 | 30 | Yes | Lost | Imp. | Abs. | Imp. | Abs. | Imp. | Imp. | .15 | None | Health good; working. |
| 19. T.M. | 69 | F | 138 | 4 | 10 | 4.0 | 81 | 22 | 100 | 32 | 32 | No | Poor | Imp. | Abs. | Imp. | N | or. | Nor. | .10 | Art. scler.; bronchopneu. | Blood status good; not working |
| 20. F.N. | 67 | F | 116 | 4 | 20 | 4.7 | 88 | .. | .. | .. | .. | Yes | N | or. | N | or. | N | or. | Nor. | .20 | Diabetes; thyrotox.; thyroidec. | Health good; working. |
| 21. M.F.* | 76 | F | 156 | 2 | 20 | 4.5 | 90 | .. | .. | .. | .. | Yes | Poor | Imp. | Abs. | Abs. | Dim. | Dim. | Nor. | .40 | Art. scler. | Health good; not working. |
| 22. M.O-C. | 43 | F | 97 | 2 | 20 | 4.6 | 94 | .. | .. | .. | .. | Yes | Poor | Poor | Dim. | Dim. | Dim. | Dim. | Nor. | .40 | None | Health good; working. |
| 23. G.P. | 53 | F | 137 | 2 | 20 | 4.4 | 85 | 43 | 105 | 33 | 31 | Nor. | N | or. | N | or. | N | or. | Nor. | .40 | Chr. inf. arthritis; bronchopneu. | Health good; working. |
| 24. H.P. | 68 | F | 112 | 2 | 20 | 4.3 | 88 | .. | .. | .. | .. | No | Poor | Poor | Abs. | Abs. | Abs. | Abs. | Nor. | .40 | Chr. inf. arthritis; Type III pneu. | 2 Gall bladder operations. Died. |
| 25. H.R. | 55 | M | 112 | 3 | 20 | 4.0 | 80 | 39 | 93 | 29 | 31 | Yes | N | or. | N | or. | N | or. | Nor. | .30 | None | Health good; working. |
| 26. M.R. | 66 | M | 80 | 3 | 20 | 4.7 | 94 | .. | 96 | 33 | 34 | Yes | Poor | Imp. | Dim. | Imp. | Abs. | Imp. | Nor. | .30 | Hyp. prostate; prostatec.; art. scler. | Health good; recovering from oper. |
| 27. L.M.S. | 68 | F | 100 | 3–4 | 20 | 3.8 | 78 | .. | .. | .. | .. | No | Poor | Poor | Abs. | Abs. | Abs. | Abs. | Same | .40 | Myxedema; cat. jaund.; chr. gall bl. | Blood status good; not working. |
| 28. M.S. | 50 | F | 117 | 3 | 20 | 4.5 | 90 | 45 | 105 | 34 | 32 | Yes | N | or | N | or. | N | or. | Nor. | .30 | Complete loss of hair; myxedema | Health good; working. |
| 29. M.Wa. | 74 | F | 131 | 2 | 20 | 4.5 | 86 | .. | .. | .. | .. | Yes | Poor | Poor | Abs. | Abs. | Abs. | Abs. | Nor. | .40 | Chr. inf. arth.; cirr. liver; frac. femur | Blood status good. |
| 30. M.We. | 73 | F | 121 | 2 | 20 | 4.6 | 94 | 43 | 99 | 31 | 32 | No | Poor | Imp. | Dim. | Imp. | Abs. | Abs. | Nor. | .40 | Art. scler.; cardiac dis. | Blood status good; not working. |
| 31. B.W. | 34 | F | 145 | 3 | 20 | 4.3 | 88 | 42 | 95 | 33 | 35 | Nor. | N | or. | Dim. | Imp. | Dim. | Imp. | Nor. | .30 | Epilepsy; dilantin treatment | Health good; working. |
| 32. Bor. | 39 | F | 129 | 2 | 10 | 4.4 | 88 | 39 | 89 | 29 | 33 | Yes | N | or. | N | or. | N | or. | Nor. | .20 | 2 Pregnancies | Health good; working. |
| 33. K.Z. | 70 | F | 127 | 2 | 10 | 4.4 | 88 | 43 | 86 | 30 | 35 | Yes | N | or. | N | or. | N | or. | Nor. | .20 | Art. scler.; sensitivity | Health good; working. |
| 34. P.Z. | 55 | M | 72 | 3 | 20 | 4.5 | 90 | 41 | 95 | 34 | 35 | Yes | Poor | Imp. | Dim. | Imp. | Dim. | Imp. | Nor. | .30 | Art. scler. | Health good; working. |
| 35. P.F.* | 62 | F | 86 | 3 | 10 | 4.4 | 83 | .. | .. | .. | .. | Yes | Poor | Imp. | Dim. | Imp. | Dim. | Imp. | Nor. | .20 | Art. scler. | Health good; working. |
| 36. L.A.* | 49 | F | 107 | 3 | 20 | 4.3 | 85 | .. | .. | .. | .. | Yes | Poor | Imp. | Dim. | Imp. | N | or. | Nor. | .30 | None | Health good; working. |
| 37. M.J.* | 64 | F | 102 | 3 | 20 | 4.2 | 84 | .. | .. | .. | .. | Yes | Poor | Imp. | Dim. | Imp. | N | or. | Nor. | .30 | Art. scler. | Health good; working. |
| 38. A.L.* | 69 | M | 92 | 3 | 10 | 4.2 | 84 | .. | .. | .. | .. | Yes | Abs. | Imp. | Abs. | Imp. | Abs. | Imp. | Imp. | .30 | Art. scler. | Health good; working. |
| 39. J.L.* | 51 | M | 192 | 1 | 20 | 4.7 | 86 | .. | .. | .. | .. | Yes | Abs. | Imp. | Abs. | Imp. | Abs. | Imp. | Imp. | .80 | None | Health good; working. |
| 40. J.S.* | 61 | F | 140 | 2 | 10 | 4.4 | 84 | .. | .. | .. | .. | Yes | N | or. | N | or. | N | or. | Nor. | .20 | None | Health good; working. |

TABLE 4.—FURTHER CASES TREATED WITH LILLY'S CONCENTRATED LIVER EXTRACT.

| Case. Name. | Age. Sex. | Treatment (weeks). | Interval (weeks). | Units per dose. | Aver. R.B.C. (mills. per c.mm.). | Aver. Hg. (%). | Hemat. | M.C.V. | M.C.H. | M.C.H.C. | Sub. imp. | Gait. First. | Gait. Last. | Vibratory sense. First. | Vibratory sense. Last. | Reflexes. First. | Reflexes. Last. | Mental. | Cost per week (dollars). | Complications. | End-results. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. E.B. | 64 F | 244 | 2 | 20 | 4.5 | 90 | 47 | 107 | 35 | 33 | Yes | Poor | Imp. | Abs. | Abs. | Dim. | Imp. | Imp. | 25 | Art. scler.; grippe | Health good; working. |
| 2. J.B. | 37 M | 200 | 2 | 20 | 4.8 | 94 | .. | .. | .. | .. | Yes | Nor. | | Dim. | Imp. | Nor. | | Nor. | 25 | Tb.; pneu. | Worked during 3 years' treatment. |
| 3. H.B. | 65 M | 205* | 2–6 | 20 | 4.0 | 80 | .. | .. | .. | .. | No | Poor | Poor | Dim. | Dim. | Dim. | Dim. | Nor. | 25 | Fracture tibia | Worked during 3 years' treatment. |
| 4. B.B. | 56 F | 235 | 2 | 20 | 4.8 | 95 | 44 | 88 | 29 | 32 | Yes | Nor. | | Nor. | | Nor. | | Nor. | 25 | None | Working. |
| 5. M.C. | 53 F | 235 | 2 | 20 | 4.5 | 90 | 42 | 91 | 29 | 32 | Yes | Poor | Imp. | Dim. | Imp. | Nor. | | Nor. | 25 | None | Working. |
| 6. H.E. | 75 F | 156* | 2–10 | 20 | 3.0 | 80 | 31 | 82 | 28 | 34 | Yes | Nor. | | Dim. | Dim. | Abs. | Abs. | Nor. | 25 | Art. scler.; grippe | Working. |
| 7. W.F. | 62 M | 156 | 2 | 20 | 4.2 | 85 | 45 | 105 | 33 | 31 | Yes | Nor. | | Dim. | Dim. | Dim. | Dim. | Imp. | 25 | Syph.; pneu. | Not working. |
| 8. E.G. | 78 M | 235* | 2–10 | 20 | 4.2 | 88 | 38 | 102 | 34 | 33 | Yes | Nor. | | Dim. | Imp. | Dim. | Imp. | Nor. | 25 | Art. scler.; cancer of penis—removed | Not working. |
| 9. F.K. | 53 F | 180 | 3 | 20 | 4.5 | 90 | 44 | 88 | 29 | 33 | Yes | Poor | Imp. | Abs. | Abs. | Abs. | Abs. | Imp. | 25 | None | Working; was completely disoriented at onset of treatment. |
| 10. A.M. | 52 F | 204 | 2 | 20 | 4.3 | 88 | 42 | 97 | 31 | 32 | Yes | Nor. | | Nor. | | Nor. | | Nor. | 25 | Varices removed | Working. |
| 11. M.M. | 56 F | 224 | 2 | 20 | 4.7 | 96 | 41 | 91 | 31 | 35 | Yes | Nor. | | Nor. | | Nor. | | Nor. | 25 | None | Working. |
| 12. D.S. | 66 M | 100 | 2 | 20 | 4.4 | 90 | 47 | 110 | 30 | 26 | Yes | Nor. | | Dim. | Dim. | Nor. | | Nor. | 25 | None | Working. |

* Attendance very irregular.

**Discussion.** If other workers agree with our findings and those of Murphy and Howard,[20] that very concentrated forms of liver extract are efficacious, the benefits derived by patient and physician should prove to be considerable. First, the patient is spared a very considerable amount of discomfort, 5-cc. doses being more uncomfortable than the 1-cc. dose. Second, the expense of Reticulogen is not notably larger than that of Lilly's Concentrated Liver Extract and both these preparations compare favorably in price with any of the others.* Third, with the more intelligent patients and particularly those in private practice, a large saving is effected by the fact that some member of the family can be taught to give 1-cc. doses, thus saving the expense involved in house or office visits. Under these conditions it has been found to be practical and safe to see the patient once in 2 or 3 months for physical examination and blood count. Fourth, there is considerable saving to the physician and the dispensary because the smaller syringes and needles are less expensive than the larger ones used for the larger doses. Fifth, there is a large saving in time in the clinic patients since they are not required to undress for injections of the concentrated extracts—they can be made in the deltoid region instead of in the buttock.

A fairly comprehensive review of the literature in English, French, German and Italian leads us to suspect that the use of very concentrated (1-cc. dose) extracts is still not widespread. This seems to be due to the fear that the concentrated form lacks some substance which is contained in the less concentrated extracts. This hypothetical substance has been said to exert a beneficial, or at least a protective effect particularly on the neural lesions. It is not our experience that this medication (Reticulogen) is lacking in this protective factor, since nearly all of our patients have received as much benefit as could be expected from any extract. In those instances where more than one extract have been used the results have been as good in this respect with the very concentrated medication as with the more dilute types.

**Summary.** 1. Forty cases of pernicious anemia have been treated with a very concentrated form of liver extract—"Reticulogen."

2. Thirty-five have been followed for periods of from 2 to 4 years.

3. Control cases who have been kept on a less concentrated form of extract have been followed over the same period.

4. Further control is offered by the fact that 12 of these 40 cases had been previously treated with oral preparations and 12 had been treated with a less concentrated form of intramuscular liver extract.

5. Red blood cell and hemoglobin levels have been maintained at satisfactory figures.

6. Neural symptoms and signs have been controlled or actually improved in a vast majority of cases.

7. Patients have been able to continue work in most instances,

* Exact information as to cost of these medications is furnished in tables.

and in others, incapacitated persons have been returned to their occupations.

8. Evidence is submitted that patients under this form of therapy are able to combat successfully many types of acute and chronic disease almost as effectively as the average population.

9. The cost of this preparation is not prohibitive, and certain savings can be made because it is more easily administered than the less concentrated preparations.

Our thanks are offered to the technical staff of the hematology laboratory for their coöperation.

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## THE VIABILITY OF THE SPIROCHETES OF SYPHILIS AND YAWS IN DESICCATED BLOOD SERUM.*†

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In both civil and military medical practice, transfusions are being made to an increasing extent with refrigerated whole blood and with

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blood serum or plasma which has been stored in the liquid or desiccated state. Since, under conditions of emergency, it may not always be possible carefully to select blood donors with respect to their freedom from syphilis, experiments were designed to determine the probable limits of safety, as regards the transmission of syphilis, in the use of such material for transfusion.

In a previous paper,[12] experiments dealing with the duration of infectivity of *Treponema pallidum* in citrated whole blood stored under conditions obtaining in blood banks were reported. In those experiments, an emulsion of virulent *T. pallidum* was added to either human or rabbit blood, and the blood stored at 2 to 4° C. Rabbits were inoculated with portions of the mixture before and at various intervals after refrigeration. Animals inoculated immediately and after 12 hours' refrigeration of the mixture, developed typical syphilitic lesions. In rabbits inoculated at 24 and 48 hours, the incubation period of the disease was prolonged, and some animals escaped infection. Animals inoculated at 72 hours and later were not infected. In a somewhat similar experiment, Bloch[2] obtained an infection at 72 hours but not later. From those experiments the conclusions were drawn that under conditions obtaining in blood banks, *T. pallidum* undergoes progressive deterioration during the storage period; that there is a corresponding reduction in the risk of transmitting syphilis by transfusion; and that it is probable that blood stored for 4 days or longer, even though taken from a syphilitic donor, can no longer transmit this disease.

The present paper is concerned with the infectivity of *T. pallidum* and *T. pertenue* in blood serum after freezing and desiccation. In brief, the experiments indicate that these organisms do not survive the drying process.

*Preliminary Observations.* Several years ago, the senior author noted that while *T. pallidum* would survive for long periods when stored in the frozen state at approximately −76° C., it commonly was promptly killed when desiccated from the frozen state.[11] In those studies, emulsions rich in treponemes were prepared from syphilitic lesions of the rabbit's testis. The emulsions were frozen rapidly in a solid carbon dioxide-alcohol mixture, and then desiccated according to the technique recommended by Swift[10] and modified by Sawyer, Lloyd, and Kitchen,[8] in which drying is carried out in a glass desiccator *in vacuo* in the presence of concentrated sulphuric acid.

More than 30 specimens from as many different sources were examined by dark-field after rehydration. In every instance, the spirochetes were badly distorted, apparently reduced in number, and none was motile. The infectivity for rabbits of 10 specimens was tested both before and after freezing and desiccation. The animals inoculated with the fresh material developed typical syphilitic lesions within the usual incubation period of the experimental disease. Nine of

the 10 specimens inoculated at various intervals after freezing and drying produced no lesions in the inoculated rabbits. One specimen tested 24 hours after the beginning of desiccation proved to be infective for 2 rabbits, although the incubation period of the experimental disease in these animals was much prolonged. Since that was the only instance, in both these and subsequent experiments, in which survival of treponemes was noted, this exceptional result is attributed to incomplete dehydration of the specimen within the 24-hour drying period. One other specimen tested after 24 hours' desiccation was non-infective for rabbits.

*Recent Experiments.* The preliminary experiments cited above were made for the purpose of finding a method of preserving the virulence of spirochetes *in vitro*. When it was obvious that freezing and drying did not provide a practical method for accomplishing this end, additional evidence regarding the non-infectivity of the material was not sought. The present experiments were carried out more meticulously, in a manner calculated to give the spirochete the best chance of survival.

**Experimental Methods.** The experiments were made at two different times, in the spring and in the fall of 1940. Except for minor variations, the procedure was the same for each experiment. Normal adult male rabbits were inoculated in each testis with the Nichols strain of *T. pallidum*. When a syphilitic orchitis was fully developed, the testes were removed and used in the preparation of the test material.* The day on which the desiccation was to be begun, each source animal was bled about 60 cc. from the heart. The blood was defibrinated, centrifuged, and the serum used for preparation of the mixture. The excised testes of each rabbit were emulsified in a mortar with sand with an amount of serum from the same animal equal to the weight of the two testes. This mixture was centrifuged ughtly in order to throw down the gross tissue particles, and the supernatant fluid was used as the test material. This was always rich in actively motile *T. pallidum*. About 1 cc. of the supernatant was set aside for subsequent inoculation, and the remainder carried through the freezing and drying process.

Desiccation of the serum-spirochete mixture was carried out under the direction of one of us (J. H. B.) by the method described by Bauer and Pickels.[1] Approximately 5 to 6 cc. amounts were distributed into 50 cc. cylindrical vials with long narrow necks. The vials were then placed on their sides in a bath containing carbon dioxide ice and alcohol, and spun on their long axis in such a manner that the fluid inside froze in a thin layer on the sides of the vial. While the vials were still at the temperature of the solid carbon dioxide-alcohol bath, they were attached to a high vacuum line and lowered into a cabinet, the temperature of which was maintained at $-18°$ C. Water was removed from the material rapidly, so that it appeared to be dry within a few moments. The tubes remained attached to the vacuum line for 60 hours, during which time the moisture in the vacuum system was removed by means of a special chamber held at $-70°$ C. The cold trap was then removed, and drying continued *in vacuo* for 24 hours longer by introducing into the system a receptacle containing phosphorus

* The preparation of the test emulsion, the freezing and drying procedures, and the inoculation of the control animals were carried out in New York. Other phases of the experiments, including the long-term observation of animals, were carried out in Baltimore.

pentoxide. The pressure in the apparatus fell rapidly to 5 to 10 microns of mercury at the beginning of desiccation, and eventually reached a pressure of 0.5 micron of mercury. These procedures are believed to promote a high degree of dehydration. After drying was completed, nitrogen dried with calcium sulphide was allowed to flow into the vials, and the necks of the vials were sealed off with a flame. Subsequently, except for about 4 hours during which the vials were in transit, they were kept at refrigerator temperature until used. In the first experiment, the material was dried with the cold trap for 24 hours, and for 24 hours with phosphorus pentoxide.

TABLE 1.—INFECTIVITY OF *T. pallidum* IN RABBIT BLOOD SERUM BEFORE AND 3 DAYS AFTER DESICCATION.

| Source of material: | Results of inoculation of fresh material intratesticularly and intracutaneously. | | | | Results of inoculation of desiccated material intratesticularly, intracutaneously and intraperitoneally. | | | |
|---|---|---|---|---|---|---|---|---|
| Rabbit No. | Rabbit No. | Total amount of inoculum, cc. | Results. | Incubation period in days. | Rabbit No. | Total amount of inoculum, cc. | Results. | Results of lymph node transfer. |
| 9–79 | 1 | 0.4 | Pos. | 13 | 13 | 3.0 | Neg. | Neg. |
| | | | | | 14 | 3.0 | " | " |
| 9–81 | 2 | 0.4 | " | 41 | 15 | 2.5 | " | " |
| | | | | | 16 | 2.5 | " | " |
| 10–01 | 3 | 0.4 | " | 13 | 17 | 4.0 | "* | . . |
| | | | | | 18 | 4.0 | " | Neg. |

* Died in 23 days.

After the vials containing the test material had been frozen and attached to the drying apparatus, a control animal was inoculated with portions of each specimen which had not been frozen and dried. In the first experiment, each control animal was inoculated in the right testis with 0.2 cc. of fresh material, and intracutaneously on the back with 0.1 cc. at each of two sites. In the second experiment, control animals were inoculated in the testis with only 0.1 cc. intracutaneously at only one site. Dark-field examinations of the fresh material after the inoculations were completed showed numerous actively motile treponemes in each specimen.

The infectivity of the dried specimens was tested in the first experiment 3 days after desiccation was started and 5 days after, in the second experiment. The dried material was rehydrated to its original volume by the addition of sterile distilled water. Each specimen was then examined carefully under the dark-field microscope. The entire amount of material from one source animal was divided into two equal portions, and each inoculated into one test animal. In the first experiment, 0.5 cc. was inoculated into one testis, 0.2 cc. intracutaneously at two sites on the back, and the remainder injected intraperitoneally. In the second experiment, the same procedure was followed except 0.2 cc. was inoculated at each of 12 sites on the back.

The test animals were examined at least twice weekly for testicular, skin, bone, and eye lesions for a period of 90 days. At the end of this period, the

popliteal nodes from each pair of animals were removed, pooled, and injected into one testis of each of two normal rabbits which, in turn, were observed in a similar manner for 90 days. Three rabbits inoculated with desiccated material died before the end of the 90-day observation period, at 23, 21, and 75 days, respectively. All were without lesions suggestive of syphilis. The popliteal nodes of the latter two were transferred, within a few hours after death, to normal rabbits which likewise remained negative.

The experiments with *T. pertenue* were carried out in an identical manner to those just described. A strain of yaws spirochetes (strain YC) isolated by the senior author in Jamaica was used throughout.

TABLE 2.—INFECTIVITY OF *T. pallidum* IN RABBIT BLOOD SERUM BEFORE AND 5 DAYS AFTER DESICCATION.

| Source of material: | Results of inoculation of fresh material intratesticularly and intracutaneously. | | | | Results of inoculation of desiccated material intratesticularly, intracutaneously and intraperitoneally. | | | |
|---|---|---|---|---|---|---|---|---|
| Rabbit No. | Rabbit No. | Total amount of inoculum, cc. | Results. | Incubation period in days. | Rabbit No. | Total amount of inoculum, cc. | Results. | Results of lymph node transfer. |
| 10–31 | 4 | 0.2 | Pos. | 14 | 19 | 13.0 | Neg | Neg. |
| | | | | | 20 | 13.0 | " | " |
| 10–32 | 5 | 0.2 | " | 17 | 21 | 12.0 | "* | " |
| | | | | | 22 | 12.0 | " | " |
| 10–33 | 6 | 0.2 | " | 18 | 23 | 7.5 | "† | " |
| | | | | | 24 | 7.5 | " | " |
| 10–51 | 7 | 0.2 | " | 13 | 25 | 6.0 | " | " |
| | | | | | 26 | 6.0 | " | " |
| 10–53 | 8 | 0.2 | " | 27 | 27 | 7.5 | " | " |
| | | | | | 28 | 7.5 | " | " |
| 10–55 | 9 | 0.2 | " | 14 | 29 | 10.0 | " | " |
| | | | | | 30 | 10.0 | " | " |

* Died in 21 days. † Died in 75 days.

**Results.** *T. pallidum.* The protocols of these experiments are shown in Tables 1 and 2. In each instance animals inoculated with fresh material which had not been desiccated developed typical syphilitic lesions of the testis and skin within the usual incubation period of the disease. *T. pallidum* was demonstrated in the lesions of each animal. In most of the rabbits, the incubation period was unusually short, indicating that the test material was highly potent.

No animal inoculated with desiccated material developed any evidence of syphilitic infection despite the fact that each was

injected with from 6 to 65 times the dose given the control animals. That symptomless infection did not occur is indicated by the fact that the lymph nodes of the inoculated animals were not infectious for normal rabbits. Two rabbits (Nos. 24 and 25) developed small erythematous lesions at the sites of intracutaneous inoculation. Careful study of these by dark-field examination and by transfer of the lesions to normal rabbits failed to reveal *T. pallidum*. Since the testis of these animals remained negative, and subsequent lymph node transfer was negative, the lesions were regarded as non-syphilitic in origin.

Dark-field microscopic examination of the rehydrated material showed that many of the treponemes were badly distorted, being shriveled in appearance with the spirals quite irregular, in contrast to the regular configuration of fresh *T. pallidum*. It is of interest, however, that in each specimen there were some fairly normal-looking treponemes, and in several specimens approximately one-third of the spirochetes appeared not to have been appreciably altered in their morphologic characteristics. None was motile. There seemed to be some decrease in the number of treponemes in each rehydrated specimen as compared with the same specimen before desiccation. Since no actual counts were made, this point cannot be definitely established. Perhaps some organisms were distorted or fragmented beyond recognition.

TABLE 3.—INFECTIVITY OF *T. pertenue* IN RABBIT BLOOD SERUM BEFORE AND AFTER DESICCATION.

| Source of material: | Results of inoculation of fresh material intratesticularly and intracutaneously. | | | | Results of inoculation of desiccated material intratesticularly, intracutaneously and intraperitoneally. | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Rabbit No. | Rabbit No. | Total amount of inoculum, cc. | Results. | Incubation period in days. | Days after desiccation started. | Rabbit No. | Total amount of inoculum, cc. | Results. | Results of lymph node transfer. |
| 9-47 | 10 | 0.4 | Pos. | 47 | 3 | 31 | 3.5 | Neg. | Neg. |
| | | | | | 3 | 32 | 3.5 | " | " |
| 10-36 | 11 | 0.2 | " | 29 | 5 | 33 | 5.0 | " | " |
| | | | | | 5 | 34 | 5.0 | " | " |
| 10-37 | 12 | 0.2 | " | 35 | 5 | 35 | 5.5 | " | " |
| | | | | | 5 | 36 | 5.5 | " | " |

*T. pertenue.* Only a few observations on the effect of desiccation on *T. pertenue* were made, but the results are similar to those obtained with *T. pallidum* (Table 3). As is usually the case, the incubation period of the experimental disease in rabbits tended to

be longer than that observed in experimental syphilis. The lesions produced in the testis by the fresh material were typical of yaws and were dark-field positive for treponemes. No animal inoculated with rehydrated material developed any lesion suggestive of yaws, and the popliteal lymph nodes of the test animals, transferred after 90 days, failed to produce lesions in normal rabbits. As shown by dark-field microscopic examination, many of the treponemes in the rehydrated material were distorted, and none was motile. Some spirochetes were normal in appearance.

**Discussion.** Methods for the desiccation of biologic products, described many years ago by Martin[7] and by Shackel,[9] have undergone successive improvements at the hands of a number of workers.[2–6,8] The method of desiccation employed in these studies is such that many species of bacteria and filtrable viruses can be dried with only slight, if any, loss of titre. There was, nevertheless, no evidence that the spirochetes of syphilis or of yaws survived this process. The test material was rich in treponemes, and its infectivity for rabbits was high before desiccation. The spirochetes were suspended in the tissue juices and serum of the animal from which the treponemes were derived, and desiccation was begun within a short time after the source material had been removed from the animal. Three to 5 days after the beginning of desiccation, large quantities of this rehydrated spirochete-containing material were injected into normal rabbits with completely negative results.

There is no evidence to suggest that *T. pallidum* or *T. pertenue* in the human host differs materially, from the standpoint of their resistance or susceptibility to desiccation, from the strains employed in these experiments. It seems fair to assume, therefore, that *T. pallidum* and *T. pertenue* occurring naturally in human serum or plasma would likewise be killed by desiccation, and that such material would be free from the risk of transmitting syphilis, even though the donor was in an active stage of the disease. To be sure, it would not be desirable knowingly to use blood from such persons, but even when great care is exercised in eliminating syphilitic donors, this cannot always be done with certainty. Moreover, in time of emergency or under stress of active warfare, it may not be possible carefully to select donors with respect to the presence or absence of syphilis or yaws. In the use of desiccated blood serum, the risk of transmitting syphilis or yaws is probably negligible.

**Summary.** 1. In experiments made several years ago, testicular emulsions rich in *T. pallidum* were frozen and desiccated. Upon rehydration, most of the spirochetes were distorted and 9 of 10 specimens tested failed to produce lesions when inoculated into normal rabbits. One specimen tested 24 hours after drying was begun produced lesions after a long incubation period. This result is attributed to incomplete dehydration of the specimen.

2. In recent experiments, the infectivity of virulent *T. pallidum* suspended in rabbit serum was tested before and 3 to 5 days after desiccation. Material from each of 9 specimens produced lesions in rabbits before desiccation. Three to 5 days after freezing and drying in an efficient desiccating apparatus, rabbits were inoculated with from 6 to 65 times the amount used for the control animals. None of 18 rabbits inoculated with desiccated material developed a syphilitic lesion, and their lymph nodes were not infectious for normal rabbits.

3. Of 6 rabbits similarly inoculated with desiccated *T. pertenue* from 3 different sources, none developed lesions, and their lymph nodes were not infectious for normal rabbits.

**Conclusions.** *T. pallidum* and probably *T. pertenue* are commonly killed by the process of freezing and desiccation, even when the method is such that the viability of many other bacteria and viruses is retained. Transfusion of desiccated blood serum or plasma is, therefore, probably without risk as regards the transmission of syphilis or yaws, even though the material be obtained from an infected donor.

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## AN AUTOPSY SURVEY OF GASTRO-DUODENAL ULCERS IN THE PHILADELPHIA GENERAL HOSPITAL 1920–1937.*

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In past years there has been much discussion in the literature of the incidence of peptic ulcer. Over a long period, many studies have been made, without conclusive results. The lack of agreement as to the incidence of peptic ulcer is largely due to two important factors: 1, the geographic factor (Table 1), and 2, the lack of

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uniformity of method used in conducting such surveys. As a result we have encountered considerable variation in the reported figures for the total incidence of peptic ulcers as found in autopsy material. In Table 1 it may be seen that, with the exception of Grunfeld's exceedingly high percentage and Lebert's low figures based on only 200 autopsies, the reported incidence ranges from about 1% to 5%. In Bassler's[1] study of 59,450 autopsies, the largest series of autopsies cited in the literature, the incidence was 4.4%. One of

TABLE 1.—THE INCIDENCE OF PEPTIC ULCERS.

| Author. | Year. | Place of observation. | No. of cases. | % of ulcers. |
|---|---|---|---|---|
| 1. Brinton[2] | 1859 | London | .... | 5.00 |
| 2. Leube[5] | 1871 | Germany | 13,605 | 4.80 |
| 3. Ziemssen[16] | 1871 | Leipzig | .... | 4.55 |
| 4. Lebert[7] | 1876 | Germany | 200 | 0.50 |
| 5. Grunfeld[6] | 1882 | Europe | .... | 20.00 |
| 6. Berthold[2] | 1883 | Germany | .... | 2.70 |
| 7. Welch[15] | 1894 | United States | 32,052 | 5.00 |
| 8. Nolte[11] | 1900 | Germany | .... | 1.23 |
| 9. Fenwick[5] | 1900 | United States | 47,912 | 4.20 |
| 10. Dreschfeld[4] | 1907 | Baltimore, Md. | 1,000 | 0.90 |
| 11. Stahl[13] | 1907 | Germany | .... | 2.16 |
| 12. Lockwood[9] | 1913 | United States | 19,315 | 1.23 |
| 13. Bassler[1] | 1926 | United States | 59,450 | 4.40 |
| 14. Sturtevant and Shapiro[14] | 1926 | New York City | 7,700 | 2.13 |
| 15. Muller[10] | 1934 | United States | .... | 2.11 |
| 16. Portis and Jaffe[12] | 1937 | Chicago | 9,171 | 4.90 |
| 17. Gordon and Manning | 1941 | Philadelphia | 22,956 | 2.75 |
| Average (excluding Grunfeld's data) | | | | 3.10 |

TABLE 2.—DISTRIBUTION OF THE FOUR MAIN GROUPS ACCORDING TO AGE AND SEX.

*White Patients.*

| | Acute gastric. | | | | Chronic gastric. | | | | Acute duodenal. | | | | Chronic duodenal. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male. | | Female. | | Male. | | Female. | | Male. | | Female. | | Male. | | Female. | |
| Age. | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| 0–10 | 1 | 1.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10–20 | 1 | 1.2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1.2 | 0 | 0 | 0 | 0 | 0 | 0 |
| 20–30 | 0 | 0 | 2 | 5.4 | 1 | 1.7 | 0 | 0 | 2 | 2.3 | 2 | 5.9 | 0 | 0 | 0 | 0 |
| 30–40 | 7 | 8.3 | 2 | 5.4 | 5 | 7.9 | 1 | 3.6 | 10 | 11.6 | 1 | 2.9 | 4 | 11.1 | 1 | 16.7 |
| 40–50 | 22 | 26.0 | 4 | 10.4 | 10 | 16.8 | 4 | 14.3 | 17 | 19.8 | 7 | 20.5 | 8 | 22.3 | 0 | 0 |
| 50–60 | 21 | 24.5 | 5 | 13.5 | 14 | 22.3 | 7 | 25.0 | 12 | 13.9 | 3 | 8.8 | 7 | 19.4 | 1 | 16.7 |
| 60–70 | 16 | 18.7 | 9 | 24.4 | 19 | 30.2 | 7 | 25.0 | 21 | 24.5 | 10 | 29.4 | 6 | 16.7 | 0 | 0 |
| 70–80 | 13 | 15.2 | 12 | 32.5 | 9 | 14.2 | 5 | 17.8 | 18 | 21.0 | 6 | 17.6 | 10 | 27.8 | 2 | 33.3 |
| 80–90 | 4 | 4.7 | 2 | 5.4 | 5 | 7.9 | 4 | 14.3 | 5 | 5.8 | 4 | 11.8 | 1 | 2.8 | 2 | 33.3 |
| Over 90 | 0 | 0 | 1 | 2.7 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2.9 | 0 | 0 | 0 | 0 |
| Totals | 85 | | 37 | | 63 | | 28 | | 86 | | 34 | | 36 | | 6 | |

*Colored Patients.*

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0–10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 5.6 | 0 | 0 | 0 | 0 |
| 10–20 | 0 | 0 | 1 | 3.6 | 1 | 4.7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 20–30 | 2 | 4.2 | 4 | 12.9 | 0 | 0 | 1 | 14.3 | 3 | 15.8 | 5 | 27.7 | 1 | 16.7 | 0 | 0 |
| 30–40 | 10 | 20.8 | 2 | 6.4 | 4 | 19.0 | 1 | 14.3 | 5 | 26.3 | 2 | 11.1 | 2 | 33.3 | 3 | 30.0 |
| 40–50 | 16 | 33.3 | 6 | 19.4 | 7 | 33.3 | 1 | 14.3 | 6 | 47.3 | 3 | 16.7 | 2 | 33.3 | 2 | 20.0 |
| 50–60 | 12 | 25.0 | 6 | 19.4 | 4 | 19.0 | 2 | 28.6 | 2 | 10.5 | 2 | 11.1 | 1 | 16.7 | 4 | 40.0 |
| 60–70 | 4 | 8.3 | 4 | 12.9 | 5 | 23.8 | 2 | 28.6 | 2 | 10.5 | 3 | 16.7 | 0 | 0 | 0 | 0 |
| 70–80 | 4 | 8.3 | 5 | 16.1 | 0 | 0 | 0 | 0 | 1 | 5.3 | 2 | 11.1 | 0 | 0 | 1 | 10.0 |
| 80–90 | 0 | 0 | 3 | 10.3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Over 90 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Totals | 48 | | 31 | | 21 | | 7 | | 19 | | 18 | | 6 | | 10 | |

the more recent and complete studies done in this country was that of Sturtevant and Shapiro[14] from Bellevue Hospital, New York City, in which they found ulcers in 2.13% of 7700 autopsies.

From our review of the literature we have arrived at the belief that there is no "true" incidence for peptic lesions the world over. It would seem, and we shall show this to be true in part, that there is considerable variation in the incidence of ulcers with the years, at least in the area about Philadelphia, as well as with the geographic location of the study.

In an effort to supply data for the Philadelphia region, we have undertaken an analysis of the consecutive autopsies performed at the Philadelphia General Hospital for the 17-year period, 1920–1937. These data were gathered to be used in a study being conducted by the Fourth Conference of the International Society for Geographic Pathology. However, due to world conditions, the conference scheduled in Rome for June, 1940, was never held.

There are several factors peculiar to this study. The most important is the nature of the cases which come into the Philadelphia General Hospital, which is a municipal, charity institution. Many of the cases are extremely ill or moribund when admitted, making complete study impossible before death. Furthermore, as the nature of the institution considerably limits the use of special studies, not all the data which might be desired could be obtained for each case. The economic status of the patients which enter this institution is also low, hence the figures obtained from this study cannot be interpreted as being representative of a true cross-section of the population.

To complete these data we have surveyed the autopsy reports from the files of the hospital. It is important to realize that the information contained therein was compiled by various pathologists who used different terminology and criteria. Therefore, the personal element is large. However, there were available descriptions of the lesions in each instance, and we have used the reports of the autopsies, along with what clinical reports were available, in order to gain the fullest possible information about each case.

We have divided the lesions according to their location in the stomach and in the duodenum. The lesions have also been classified as acute and chronic. In all instances this latter distinction was made upon microscopic examination.

Between 1920 and 1937, 22,956 autopsies were performed at this hospital, and in this series 548 cases were found to show peptic lesions, an incidence of 2.75% for the entire series.

Table 2, presenting the age and sex distribution of lesions in both whites and negroes, has been subdivided into acute and chronic lesions in the stomach and in the duodenum. Peaks in the incidence of peptic lesions are seen in the fifth and seventh decades, the highest peak being seen in the latter decade (Charts 2*a* and 2*b*). In the

negroes, for both gastric and duodenal lesions, the peak for males is in the fifth decade, and for females, in the seventh. Part of this 20-year difference between races may be explained by the inexactness with which colored people state their age.

Chart 1 is a representation of the age distribution of peptic lesions of all types for both white and colored patients. It is to be noted that the peak of the incidence for colored patients appears about 20 years before that for white patients. This is in close relation to the average life-expectancy difference between the two races.

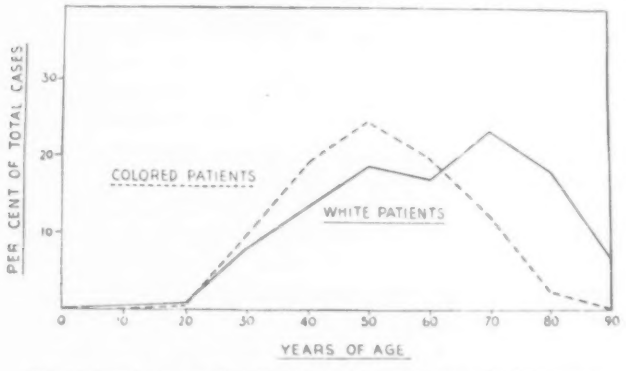


CHART 1.—Age-race distributions of peptic ulcers in 548 cases.

Table 3, analyzing the cases according to sex, race and type of lesion, shows that the ratio of colored to white is about 1 to 2.4. The hospital autopsy records give an average ratio of colored to white of 1 to 2.6. This is a significant indication that there is no racial factor operating in gastro-duodenal ulcerations in the Philadelphia region.

In this same table, the ratio between males and females is 2.1 to 1 for all types of peptic lesions. The ratio of males to females, duodenal lesions only, is 2.49 to 1, not significantly different from the ratio of all lesions. It would appear from this that the frequency of peptic lesions is twice as great in males, and that this frequency does not vary greatly with the years studied.

Table 4 was constructed for type of lesion, sex and the year in which the autopsy was performed in the hospital. We have divided the cases occurring before and after January, 1933, as we found that there was a significant difference in the occurrence of gastro-duodenal lesions before and after this date. The standard deviation for the figures found before 1933 is 0.49%; the standard deviation for those after 1933 is 0.59%. The probability that two such different groups could be drawn by chance from a homologous sampling of cases is considerably less than 1 in 100. We wish to call attention to the fact that the years 1920–1932 were within the period during which

prohibition of the sale of alcohol existed in the United States. The period 1933–1937 was without this prohibition. The significance of this fact cannot be determined accurately since records of alcoholism in the cases studied were very incomplete. It must also

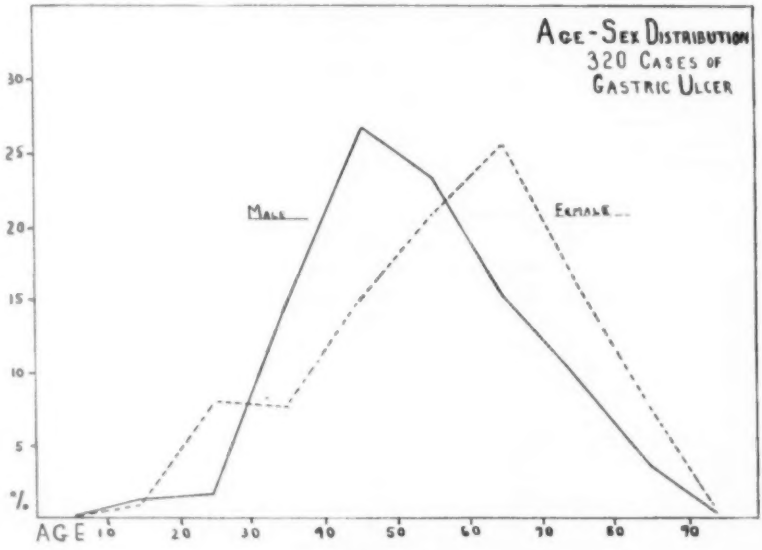


CHART 2*a*.

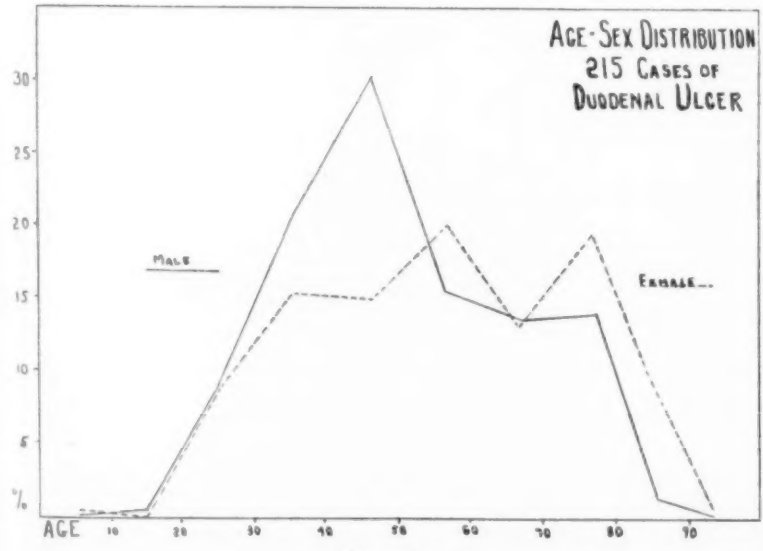


CHART 2*b*.

be remembered that this same period was one of economic insecurity and depression. Chart 3 illustrates clearly the difference between the period before 1933 and that after 1933. During this time there was no change in autopsy procedures or in the type of records available which might account for this difference.

TABLE 3.—SEX-RACE-LESION DISTRIBUTION.

| | Acute gastric. | Chronic gastric. | Acute duodenal. | Chronic duodenal. | Total. | %. |
|---|---|---|---|---|---|---|
| White males | 86 | 60 | 90 | 36 | 272 | 49.9 |
| White females | 44 | 32 | 28 | 6 | 110 | 20.2 |
| Black males | 50 | 17 | 23 | 8 | 98 | 18.0 |
| Black females | 29 | 7 | 20 | 9 | 65 | 11.9 |

TABLE 4.—ANNUAL SEX AND LESION DISTRIBUTION.

*1920–1932.*

| | Acute gastric. | | Chronic gastric. | | Acute duodenal. | | Chronic duodenal. | | % total autopsies for year. |
|---|---|---|---|---|---|---|---|---|---|
| Year. | Male. | Female. | Male. | Female. | Male. | Female. | Male. | Female. | |
| 1920 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0.23 |
| 1921 | 4 | 2 | 3 | 3 | 5 | 0 | 0 | 0 | 2.35 |
| 1922 | 2 | 0 | 1 | 1 | 1 | 3 | 0 | 2 | 1.16 |
| 1923 | 3 | 3 | 3 | 1 | 1 | 2 | 4 | 0 | 1.64 |
| 1924 | 6 | 3 | 5 | 2 | 3 | 1 | 0 | 2 | 2.00 |
| 1925 | 3 | 1 | 1 | 2 | 6 | 1 | 0 | 0 | 1.44 |
| 1926 | 7 | 2 | 4 | 1 | 5 | 1 | 0 | 2 | 2.01 |
| 1927 | 4 | 0 | 0 | 1 | 7 | 1 | 2 | 0 | 1.18 |
| 1928 | 9 | 4 | 1 | 0 | 5 | 1 | 0 | 0 | 1.65 |
| 1929 | 7 | 4 | 2 | 0 | 1 | 2 | 0 | 0 | 1.42 |
| 1930 | 5 | 4 | 1 | 2 | 5 | 2 | 2 | 1 | 1.94 |
| 1931 | 8 | 4 | 2 | 2 | 2 | 5 | 1 | 0 | 1.92 |
| 1932 | 8 | 7 | 6 | 3 | 6 | 4 | 1 | 2 | 2.90 |

Average number of cases per year: male, 11.7; female, 6.6. Average % of total autopsies for a year: 1.68.

*1933–1937.*

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1933 | 12 | 7 | 8 | 5 | 13 | 6 | 6 | 1 | 3.40 |
| 1934 | 16 | 3 | 7 | 2 | 19 | 5 | 3 | 0 | 2.85 |
| 1935 | 12 | 4 | 7 | 2 | 10 | 7 | 5 | 2 | 2.50 |
| 1936 | 13 | 10 | 15 | 5 | 13 | 6 | 5 | 2 | 3.50 |
| 1937 | 19 | 13 | 12 | 6 | 12 | 2 | 14 | 3 | 4.15 |

Average number of cases per year: male, 44.2; female, 18.2. Average % of total autopsies for a year: 3.28.

TABLE 5.—LOCATION OF LESIONS.

| | Acute gastric. | Chronic gastric. | Acute duodenal. | Chronic duodenal. | Totals. | %. |
|---|---|---|---|---|---|---|
| Near esophagus | 4 | 3 | .. | .. | 7 | 1.3 |
| Cardia | 37 | 9 | .. | .. | 46 | 8.5 |
| Fundus | 64 | 18 | .. | .. | 82 | 15.3 |
| Within 6 cm. of pylorus | 71 | 34 | .. | .. | 105 | 19.7 |
| At pylorus | 45 | 27 | .. | .. | 72 | 13.5 |
| Duodenum: First portion | .. | .. | 140 | 47 | 187 | 35.0 |
| Second portion | .. | .. | 12 | 4 | 16 | 2.9 |
| Third portion | .. | .. | 6 | 3 | 9 | 1.7 |
| More than one lesion in stomach | 77 | 30 | 20 | 5 | 132 | 24.7 |
| More than one lesion in duodenum | 17 | 6 | 51 | 8 | 82 | 15.3 |

In Table 5 the lesions were arranged according to their acute and chronic nature, and according to their location in the gastro-intestinal tract. The stomach has been divided into five portions:

1. Near the esophagus: an area which was considered to be within 2 cm. of the esophageal opening into the stomach.

2. Cardia: the upper one-third of the stomach.

3. Fundus: the portion of the stomach from below the "cardia" to within 6 cm. of the pyloric ring.

4. An area within 6 cm. of the pylorus, limited distally by the pyloric ring.

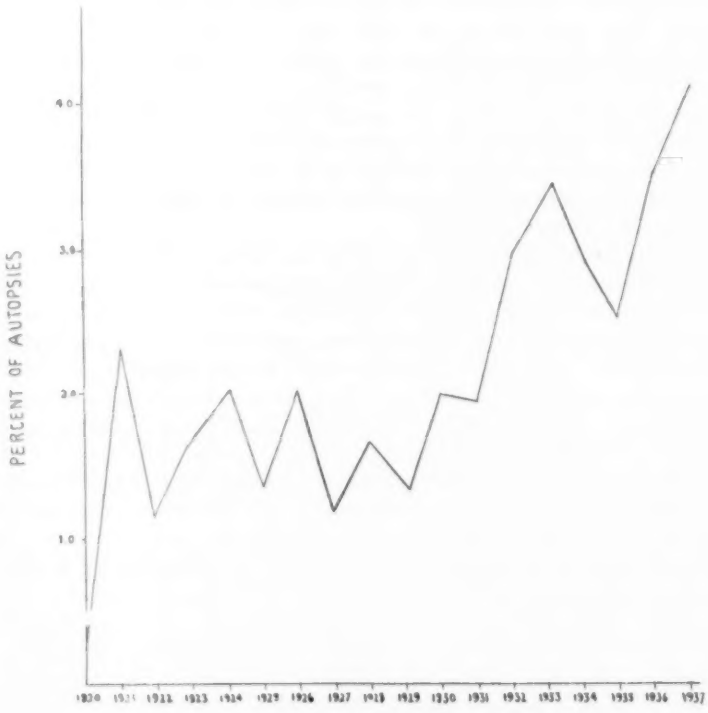


CHART 3.—Yearly distribution of peptic ulcers.

5. Pylorus: the region of the pyloric sphincter muscle and as far as the proximal edge of the duodenum.

The duodenum was divided into three portions:

1. First portion: the superior 2 inches (5 cm.).

2. Second portion: the descending portion, about 3 inches (7.5 cm.) long.

3. Third portion: in which was included the anatomic third and fourth portions, the last 5 inches (12.5 cm.) of the duodenum.

This latter inclusion of the two anatomic areas into one group was made because of the extreme rarity of lesions in this general area. The figures show that in the stomach region 83.5% of the lesions were within 6 cm. of, or at, the pylorus. In the duodenum, 88% of the lesions were in the first 2 inches (5 cm.) of the organ. This table does not include all of the 548 cases because specific information as to the location of the lesions was not available in every case.

If one desires to examine these results in terms of the three more usual divisions of the stomach, it may be done by adding the esophageal and cardiac areas, yielding 9.8%, this corresponding to the "Cardia." The "Fundus" is the same as seen in our table. The "Pylorus" amounts to the sum of the area 6 cm. away from the pyloric ring, and the pyloric ring, 33.2%. Also in Table 5 have been included figures to show the number of cases in which there occurred more than one lesion in either the stomach or duodenum. It was found that 4.7% of the gastric lesions were accompanied by other peptic lesions in the duodenum, and 4.3% of the duodenal lesions showed concomitant lesions in the stomach. The size of the ulcer was the determining factor in arriving at which lesion was of primary importance.

Because liver lesions were noted in an extremely high percentage of this series of autopsies, Table 6 was constructed to bring out this fact. Liver lesions being rather difficult to define, arbitrary division as to the degree of altered function was undertaken. "Parenchymal Degeneration" is a term variously used by the group of men performing the autopsies. Many of these cases can best be considered as terminal or postmortem change that has little importance in regard to liver function during life. In the group "Metastatic Carcinoma" have been included cases in which islands of definite malignant tissue were proven by microscopy. The amount of dysfunction that such a condition presents probably belongs with the "Chronic Passive Congestion" group in degree. Cardiac lesions being present in a large percentage of these cases, the liver categories were divided into those with, and those without, cardiac lesions. This table shows that 58% of ulcer cases were accompanied by definite liver damage. A random sampling of the autopsies at the same hospital without regard to peptic lesions showed 35% with definite liver damage. The standard error of each of these figures is about 2%. The difference between the ulcer group and the control group is 11 times the standard error. The chance of obtaining, from a homogeneous population by purely random sampling, two samples of this difference is incalculably small.

Nowhere in the literature have we found observation of this coëxistence of peptic ulcer and liver damage. The relationship between liver function and peptic ulceration has not been clearly established. However, we suggest that liver damage may be a factor in altering the local circulation of the stomach and duodenum,

thereby predisposing to peptic ulceration. This fact is further suggested by the large number of cases of cardiac damage found in relation to peptic lesions.

TABLE 6.—ACCOMPANYING LIVER LESIONS.

| | Acute gastric. | Chronic gastric. | Acute duodenal. | Chronic duodenal. | Totals. | %. |
|---|---|---|---|---|---|---|
| *Cirrhosis:* | | | | | | |
| With cardiac lesion | 11 | 8 | 14 | 5 | 38 | 7.1 |
| Without cardiac lesion | 12 | 3 | 9 | 2 | 26 | 4.8 |
| *Chronic Passive Congestion or Necrosis:* | | | | | | |
| With cardiac lesion | 52 | 12 | 30 | 10 | 104 | 19.4 |
| Without cardiac lesion | 49 | 26 | 46 | 20 | 141 | 26.4 |
| *Parenchymal Degeneration:* | | | | | | |
| With cardiac lesion | 15 | 10 | 15 | 7 | 47 | 8.8 |
| Without cardiac lesion | 45 | 26 | 34 | 14 | 119 | 22.2 |
| *Normal Liver:* | | | | | | |
| With cardiac lesion | 1 | 3 | 3 | 0 | 7 | 1.3 |
| Without cardiac lesion | 4 | 5 | 7 | 1 | 17 | 3.2 |
| *Metastatic Carcinoma:* | | | | | | |
| With cardiac lesion | 1 | 2 | 0 | 1 | 4 | 0.8 |
| Without cardiac lesion | 5 | 3 | 2 | 1 | 11 | 1.9 |

TABLE 7.—COMPLICATIONS OF PEPTIC ULCERATION.

| | Acute gastric. | Chronic gastric. | Acute duodenal. | Chronic duodenal. | Total. | %. |
|---|---|---|---|---|---|---|
| Bleeding of ulcer | 46 | 8 | 28 | 14 | 96 | 17.9 |
| Perforation of ulcer | 39 | 22 | 65 | 13 | 139 | 25.0 |
| Mucosal scars | 19 | 67 | 31 | 21 | 138 | 25.8 |
| Probable malignancy of ulcer | 6 | 0 | 0 | 0 | 6 | 1.1 |

The complications of peptic ulcer are dealt with in Table 7. Perforation occurred in 25% of the cases, and bleeding in 17.9%. The presence of mucosal scars is an indication of the healing tendency of ulcers. This was noted in 25.8% of this series. Also of note is the fact that histologic examination of the ulcers revealed but 6 cases in which there was any suggestion of malignancy in the ulcer base.

**Summary.** This study of 22,956 autopsies has shown peptic ulcers in 2.7% of the cases. There seems to be no racial difference in incidence between white and colored patients. Males show ulceration twice as frequently as females. There has been a significant increase in the observed incidence of ulcer since 1933. Liver lesions occur in ulcer cases in a significantly greater percentage of autopsies than in a random sample of this hospital's autopsy records. While the incidence of ulceration varies with the geographic locality and with the calendar years studied, the age groups most involved, namely the fifth to seventh decades, remain constant in our material.

We wish to express our sincere gratitude to Dr. M. M. Lieber for the use of his cross-index of the autopsy records of the Philadelphia General Hospital, and to thank Dr. J. H. Clark for making available these records.

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## THE USE OF 2-SULFANILAMIDOPYRAZINE IN PNEUMOCOCCAL PNEUMONIA.

### A PRELIMINARY REPORT.*

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DOMAGK's[3] discovery of the chemotherapeutic value of sulfanilamide has opened a new field of medicine. Subsequent investigations have broadened the usefulness of this type of therapy, largely through the development of other derivatives. Several thousand such compounds can be synthesized by introducing substituent groups in the molecule. Clinical use of a few of them has followed observations of their antibacterial activity and relative toxicity for animals. Thus, sulfapyridine and sulfathiazole have gained wide

* This study was aided by a grant in honor of Craig Yeiser.

acceptance as useful and relatively safe agents in pneumonia therapy. A third, sulfadiazine[5,7] has shown promise of clinical usefulness in pneumococcal pneumonia. Still another derivative, 2-sulfanilamidopyrazine* ("sulfapyrazine"), is the subject of this study. It interested us particularly because of a previous observation that pyrazine monocarboxylic acid is less toxic than the corresponding pyridine carboxylic acid. As there have been no clinical reports published on the use of sulfapyrazine, we offer this brief preliminary study in hope that it will stimulate further trial.

2-Sulfanilamidopyrazine ("sulfapyrazine") is a colorless, tasteless, crystalline substance, melting at 255° to 257° C. It is slightly soluble in water, but dissolves readily in weakly alkaline solutions. Its sodium salt, sodium 2-sulfanilamidopyrazine monohydrate, is freely soluble and is less strongly alkaline than the sodium salts of sulfapyridine, sulfathiazole and sulfadiazine (pH 9.3, 10.7, 10.0, 10.2, respectively, for 10% solutions in physiologic saline).

Single doses of 1 gm. per kg. (as the sodium salt, but figured on the basis of the free drug) were injected intraperitoneally into mice. Death followed usually within 24 hours. Doses of 0.5 gm. or less per kilo of body weight were tolerated without ill-effects. Four dogs were given 2 gm. of the drug daily for 40 days. They not only tolerated these doses well but gained weight during the period of observation. Further observations indicate a low order of toxicity in rats, dogs and monkeys, and will be reported fully in another communication.

Single dose studies, employing 4 gm. by mouth per dose, were made on 6 convalescent hospital patients. Frequent determinations of the blood level disclosed the maximum between 4 and 8 hours after administration of the drug. No abnormal symptoms were detected when the drug was given to patients in amounts of 8 to 12 gm. daily for a short period of time. Following these observations, the drug was administered to 22 pneumonia patients, the responses of which form the basis of this report. Almost simultaneously with our editorial statement about its use in pneumonia,[4] Raiziss reported that he had found sulfapyrazine effective against Type II pneumococcus infection in mice.[6]

The great majority of the patients had typical pneumonia, although a few had given atypical histories; all had unequivocal clinical or roentgenographic signs of consolidation. Because of the uncertainty concerning the efficacy of the drug, only those patients were selected who, on admission, did not seem to require intravenous therapeutic agents. All 22 patients recovered. Pertinent data concerning these patients are recorded in the table.

The drug was administered orally in each instance. An initial dose of 2 or 4 gm. was employed; thereafter, 1 gm. was given every

* This drug was synthesized and supplied by Dr. R. C. Ellingson of Mead Johnson & Co.

4 hours until the patient was free of fever for 2 days. Blood "sulfapyrazine" determinations were made at frequent intervals, employing the method of Bratton and Marshall.[2] As expected from preliminary observations, the level of the drug in the blood stream rarely was higher than 3 mg. per 100 cc. when the above dosage was employed; in several instances, recovery occurred when only traces were demonstrable in the blood. The drug rapidly disappeared from the blood after administration.

TABLE 1.—ANALYSIS OF PNEUMONIA CASES TREATED WITH SULFAPYRAZINE.

| Sex. | Color. | Age. | Type. | Blood culture. | Dosage. | | Highest level. | Lobe involved. | Day of disease. | Outcome. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Grams. | Days. | | | | |
| M | W | 57 | XXXII | Neg. | 28 | 5 | 3.2 | LL | 2 | Well |
| M | W | 28 | VII | Neg. | 34 | 6 | 2.1 | RU | 3 | Well |
| M | W | 19 | I | Neg. | 28 | 5 | Trace | RL | 1 | Well |
| M | C | 21 | XIV | Neg. | 27 | 5 | Trace | RL | 3 | Well |
| M | W | 17 | VII | Neg. | 25 | 4 | 1.6 | RL | 3 | Well |
| M | C | 33 | V | Neg. | 23 | 5 | Trace | LL | 1 | Well |
| M | C | 27 | VIII | Neg. | 25 | 5 | 2.2 | LL | 1 | Well |
| M | C | 18 | XXVII and "Carver" | Neg. | 26 | 5 | 2.1 | LL | 5 | Well |
| M | W | 14 | I | Pos. | 27 | 5 | 2.3 | LL | 3 | Well |
| M | C | 39 | III | Neg. | 18 | 3 | 2.5 | RM RL | 6 | Well |
| M | C | 54 | VIII | Neg. | 24 | 4 | Trace | LL | 1 | Well |
| M | C | 38 | I | Neg. | 12* | 2 | 2.3 | RU | 3 | Well |
| F | W | 63 | VIII | Pos. | 45 | 7 | 2.9 | RU | 4 | Well |
| F | W | 34 | II | Neg. | 37 | 6 | 1.5 | RL | 3 | Well |
| M | W | 19 | XXVII | Neg. | 24 | 4 | 1.7 | LL | 3 | Well |
| M | W | 42 | I | Neg. | 45 | 8 | 2.9 | LL | 4 | Well |
| F | W | 29 | VII | Neg. | 14 | 3 | 1.7 | LL | 3 | Well |
| F | W | 17 | V | Neg. | 24 | 4 | 2.4 | RL | 4 | Well |
| M | C | 29 | I | Neg. | 34 | 6 | 2.5 | RUML | 4 | Well |
| M | W | 64 | I | Neg. | 26 | 4 | 3.5 | RL | 3 | Well |
| F | C | 17 | V | Neg. | 25 | 4 | 3.3 | LL | 3 | Well |
| M | W | 52 | I | Pos. | 29 | 4 | 4.6 | RM | 5 | Well |

* This patient's temperature had fallen to normal after 12 gm. of sulfapyrazine. At this time, he was inadvertently given sulfathiazole; consequently, therapy was continued with sulfathiazole.

Within 18 hours after the institution of treatment, all of the patients showed clinical improvement. In 4 instances, the diminution or disappearance of pleural pain was the first improvement noted subjectively; more often, improvement was general and less easily defined. In 12 of the patients, a critical fall of temperature occurred 12 to 24 hours following the administration of the first dose. In no instance was there a recrudescence of fever after the temperature had fallen below 100° F. (rectal). Three of the patients had positive blood cultures at the time treatment was begun; 18 hours later, blood cultures in media which had been enriched with

para-amino benzoic acid were sterile. None of the patients had purulent complications either before or after treatment.

Untoward reactions to the drug were infrequent, if present, in this series. No patient complained of nausea and none vomited. Mental symptoms were observed in 2 patients; these consisted of hallucinations and persecutory delusions occurring after 48 hours of treatment. Both improved rapidly after discontinuance of the drug and had no memory of the unpleasant incident. Subsequent administration of the drug in the same doses failed to duplicate this clinical picture of disorientation or hallucination. Daily examination of the cellular elements of the blood disclosed no apparent effects. Similarly, frequent examinations of the urine and urinary sediment did not reveal the presence of blood or evidence of depression of renal function. Skin rashes did not occur in this series.

**Summary.** A new derivative of sulfanilamide, 2-sulfanilamidopyrazine, has been given clinical trial in pneumococcal pneumonia. Twenty-two selected patients received the drug by mouth. All showed prompt improvement and ultimate recovery, with no significant signs of toxicity. The drug is apparently tolerated well and it deserves further clinical trial.

By the time the proof of this article was returned, the authors had treated 10 additional patients, of whom 2 were bacteremic. All recovered and had no signs of toxicity following the administration of sulfapyrazine.

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## THE CAPILLARIES IN MYXEDEMA.

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and

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The heart in myxedema has been fully described by one of us[2a–c] in 1918–19, and the symptomatology, which has been verified by many authors in the meantime, may be taken for granted. Less attention has been paid to the peripheral circulation in myxedema. Recently we have devoted ourselves to the study of the capillaries in connection with this disease. We have had the opportunity of

observing 8 myxedema patients, some of them for several years. They were all women, between 30 and 62 years of age.

We studied the capillaries of the ungual limbus previous to, during and subsequent to thyroidin treatment. In 7 of the 8 patients the capillaries showed a uniform characteristic picture. They were fewer in number and very narrow (Fig. I). In some instances there was only a barely recognizable, fine line to be seen in the microscopic field. Details, particularly a flow, could not be distinguished. In those places where the capillaries were not narrowed there was a brittle mass filling them, with a great many intervening gaps. In other places, only the small loop was seen, while the straight portions were invisible. In those instances in which the entire length of the capillary vessel was recognizable both limbs were in almost every case very straight with no tortuous or crooked portions. The two limbs were very close together and the intermediary part was pointed and sharply bent. The flow, as far as any was recognizable, was apparently rapid. The width of the venous and arterial part did not show much difference; sometimes none at all. In some cases the whole picture was somewhat hazy. It was as though the details were slightly veiled. Since the number of capillaries was small the intermediary spaces with no vessels were clearly visible. We give here the case history of one of the patients who was under our observation for 4 years.

**Case Report.** Mrs. H., aged 33, weighed 67 kilos. She said that she had always been healthy, and had had 4 normal deliveries. Menstruation has always been regular without any trouble. Recently she has gained markedly in weight. Face and hands had become swollen, her movements strikingly slow. She was impressed by the fact that the housework became more and more difficult for her. Sometimes she had pains in the back and legs and a feeling of tightening and oppression in the region of the heart. Her voice had become lower and coarse. She, moreover, complained that she was continually cold and constipated. Physical examination: The patient is small and looks rather pasty. The skin is pale and also rough and cold to the touch. Judging by her face, she is older than would be expected for her age. The pharynx is without any abnormalities, the tongue is thick, the heart enlarged both right and left sides, the heart sounds are clear but extremely muffled, the pulse is regular, 56 per minute. Blood pressure 95/60 mm. Hg. On the screen, we saw that the action of the heart was slow and that the contractions were superficial. Lungs, normal. Abdomen, normal. The extremities are sensitive to pressure, the skin is rough, but there is no edema. The reflex responses are slow. The pupils react normally to light. Blood picture: hemoglobin, 82%; erythrocytes, 4,200,000; leukocytes, 5000. Basal metabolic rate, −29%. Blood cholesterol, 423 mg. per 100 cc. Sella turcica, without any peculiarities.

Similar findings were obtained in the other 6 patients. During thyroidin treatment the number of capillaries increased and their limbs became wider (Fig. II, *a–c*). While they had been straight previous to the treatment, they now became curved and tortuous. The venous portion was sometimes markedly distended and the bloodflow slowed down so that stagnation was brought about.

It is worthy of note that the changes of the capillary picture were by no means in proportion to the clinical improvement. In some instances the capillary picture varied in such a way that in some fingers wide capillaries were found while in others they were narrow. No parallelism between the decreasing circulation time and capillary dilation was noted (tested by means of a 20% magnesium sulphate injection). Although the bloodflow became more

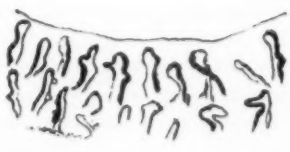
Ia

IIa

Ib

IIb

Ic



IIc

FIG. I FIG. II

FIG. I.—Capillaries of the ungual limbus of 3 myxedema patients before thyroidin treatment.

FIG. II.—Capillaries of the ungual limbus of 3 myxedema patients after thyroidin treatment.

rapid, the capillaries, to begin with, often remained narrow. Only later did they become wider, but no regularity could be observed in this respect. Thus, for instance, in one of the patients, the capillaries were very narrow, while the circulation time was normal.

An explanation of this discrepancy might be that the circulation time does not depend exclusively on the capillary dilation, but is also linked to the condition of the arteriovenous anastomoses. Opening the arteriovenous anastomoses brings about considerable

increase of the circulatory speed without the cross-section of the capillary bed being considerably enlarged. This has also been verified by Michael's and Buschke's[1] investigations who found the capillaries to be surprisingly narrowed in Graves' disease, a condition similar to that observed by us in myxedema. Since, however, these two conditions are associated with the opposite circulatory symptoms, particularly as concerns the circulatory speed, it should be concluded that these symptoms are produced by the opposite behavior of the arteriovenous anastomoses, not, however, by that of the capillaries. It should be assumed that in Graves' disease with its abnormally increased oxygen requirement of the tissues and increased circulatory speed the arteriovenous anastomoses are open. In the myxedema patient with his reduced oxygen requirement in the tissues and reduced circulatory speed, the capillaries are certainly narrowed, but, in addition, the arteriovenous anastomoses must, as a consequence, also be closed. If, as the result of thyroidin treatment, the $O_2$ requirement rises again so that an increased blood supply of the tissues becomes necessary, this increase may be brought about by dilation of the capillaries as well as by the opening of the arteriovenous anastomoses. Both may, however, occur in interaction with one another. Thus it becomes comprehensible that the capillary picture is not always parallel to the increase of the circulatory speed.

The question as to whether the control of the peripheral portion of the circulation (capillaries, arteriovenous anastomoses) is executed by the thyroid hormone is not easily decided. Since, apparently, the arteriovenous anastomoses show an opposite action in Graves' disease and myxedema, it should be assumed that it is actually the thyroid hormone that is the responsible factor in this process. This would mean that the same hormone that on the one hand sets the circulatory machinery in motion, increases the number of its revolutions (the minute volume as well as the amount of blood in circulation) which shortly increases the actual work performed by the heart. On the other hand, this hormone must be held responsible for the less powerful action of the heart. That the capillary function might also be subject to the activity of the thyroid hormone, is highly improbable. This would also be contradictory to their uniform behavior in Graves' disease and myxedema.

It is a well-known fact that the cardiac muscle in myxedema contains much fluid matter (Zondek). Some of our patients who complained of angina-like heart trouble were improved by this therapy. The optimal dosage varied greatly as to the individual case (from 0.3 to 0.4 gm. thyroidin weekly up to 0.4 to 0.6 gm. daily). Up to the present, the stenocardiac symptoms occurring in the patients who are suffering from myxedema have been explained by their tendency to develop an early arteriosclerosis. It has been shown by animal experiments that thyroidectomy may induce severe

atheromatosis of the aorta (v. Eiselsberg, Pick and Pineles, *et al.*). The immediate response to thyroidin therapy in most cases, however, in itself supports the theory that these troubles cannot be due to arteriosclerosis. It is, in our opinion, more rational to assume that the process of swelling taking place in the cardiac muscle with the resulting pressure on the blood-vessel—which means a reduced blood supply to the cardiac muscle—is also active in bringing about the stenocardiac symptoms. It is suggested that the same narrowing of the blood-vessels which was found on the peripheral capillaries takes place in the myocardium. In this way, the beneficial effect of thyroidin is also explained.

In any case the nature of the process taking place in the blood-vessels which induces the stenocardiac paroxysm in the myxedema patient is entirely different from that which is found in sclerotic changes of the blood-vessels. This is not only evidenced by the intensity of the symptoms, which do not attain the same degree in myxedema patients as they do in connection with genuine angina pectoris, but it is also made clear by the different response to thyroidin therapy. Recent investigations have produced much elucidation insofar as it is now evident that genuine angina pectoris, in particular the so-called angina of effort, is beneficially influenced by thyroidectomy. We are, therefore, considering two different phenomena of the cardiac—circulatory apparatus.

By the way, in those patients who present the symptoms of slight stenocardia, even if there are no other symptoms of myxedema, one should always consider the possibility that their troubles may be thyrogenous in nature (abortive type of myxedema heart) (Zondek.[2d]). Particularly so, if the basal metabolic rate is lowered. In patients of this kind we occasionally found it reduced to as low as 30%. It was, however, striking that the values varied greatly. Small doses of thyroidin may now and then produce a surprisingly favorable result (0.3 to 0.4 gm.).

**Summary.** In 8 women suffering from myxedema with typical myxedema hearts, the peripheral circulatory portion was subjected to exact investigation. In 7 cases the capillaries (ungual limbus) were markedly changed, the most striking feature being pronounced narrowness of the limbs. In some instances the loops only were recognizable. The number of visible capillaries was reduced. On thyroidin administration, the capillary picture as well as the clinical symptoms and the circulation time gradually returned to normal. No parallelism, however, could be established between the behavior of the capillaries on the one hand, and the general condition and the acceleration of the circulation time on the other hand. In the light of this evidence, the conclusion may be drawn that thyroidin is active in opening the arteriovenous anastomoses. Apparently the cross-section of the anastomoses as well as that of the capillaries is

reduced in cases of myxedema, which is comprehensible in view of the abnormally reduced oxygen requirement.

In many cases myxedematous patients suffering from precordial pains similar to anginal states are likewise relieved by thyroidin administration. In this case, thyroidin is assumed to bring about a dehydration of the heart muscle (Zondek) and thus an increase in the blood supply of the heart. It is, therefore, suggested that the development of precordial pains in myxedematous patients is not, as a rule, due to sclerotic changes of the cardiac vessels, as generally assumed, but to mechanical impairment of the coronary flow.

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# BOOK REVIEWS AND NOTICES

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. *Complete Index.* Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., Professor of Medicine, University of London, etc., G. GREY TURNER, D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., Professor of Surgery, University of London, etc., JAMES YOUNG, D.S.O., M.D., F.R.C.S. (EDIN.), F.C.O.G., Professor of Obstetrics and Gynæcology, University of London, etc., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., Late Physician, Hospital for Tropical Diseases, London, and F. M. R. WALSHE, O.B.E., M.D., Sc.D., F.R.C.P., Physician in Charge of the Neurological Department, University College Hospital. Pp. 486. London: Butterworth & Co. (Publishers), Ltd., 1941. Price, $10.00.

IN spite of the difficulties of producing an Index in England, under war-time conditions, the publishers have completed this important task in such a satisfactory way that the value of the whole set is considerably enhanced. In spite of the increased costs in paper, printing and binding, the Index is issued at a lower price than the other volumes. E. K.

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THE MEDICAL ASPECT OF BOXING. By ERNST JOKL, M.D., Head of Department of Physical Education, Witwatersrand Technical College, Johannesburg, So. Africa; Consultant, Medical Aspect of Physical Education, S. A. Defense Force. Pp. 251; illustrated. Pretoria, So. Africa: J. L. Van Schaik, Ltd., 1941.

THIS monograph should be of great interest to all those connected with athletes and games of the "body contact" type. While boxing is primarily dealt with in this book, head injuries are frequent in football, or ice-hockey. Although the knock-out punch with its consequent concussion is delivered deliberately in boxing and is a hazard connected with that sport, nevertheless, a head injury is still a head injury regardless of how or in what field of athletic endeavor it is received.

"The most frequent knock-out is caused by blows to the chin, those coming somewhat from the side and from below (uppercuts) being rather more effective than blows from directly in front. They result in immediate loss of consciousness lasting for periods of variable length. From all available knowledge and experience, it is concluded that the typical knock-out blow to the chin leads to a two-phasic jerk, which affects the medullary centers. During the first phase the clivus and the anterior edge of the foramen magnum of the occipital bone are pushed against the lower portions of the pons and the upper anterior surface of the medulla oblongata; while during the second phase by virtue of a contrecoup (rebounding) effect, the medulla oblongata bounces back against the internal surface of the occipital bone and the posterior edge of the foramen magnum. It would appear that this double impact produces unconsciousness for injury to the medulla oblongata produces unconsciousness much more readily than does injury to any other part of the brain."

Although discussion of the immediate effects of a "blow sufficiently severe to produce concussion" is given, in subsequent chapters the remote sequelæ of repeated head injuries, headache, dizziness and instability in gait are described and the physiology discussed.

Other methods of knocking out an opponent by blows over the heart or solar plexus with their accompanying injuries to thoracic and abdominal organs are outlined. Each variety of injury is illustrated by case histories. A good bibliography is appended.

All in all the author develops a fairly grim case against any of the "bodily contact" sports. However, he does not have any suggestion either for improvement in the methods of conducting them or for substitution of different and possibly less dangerous types of sport. It is quite true that any of the injuries he describes can occur. But the Reviewer believes that even if these facts were carefully explained to him no real athlete would refuse to take part in such games on that account. The book is useful however in pointing out to those in charge of athletics the potential dangers concerned in any form of sport so that by careful supervision and observation of the participants repeated injuries can at least be minimized.

F. G.

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THE HEART IN PREGNANCY AND THE CHILDBEARING AGE. By BURTON E. HAMILTON, M.D., Cardiologist (since 1921) to The Boston Lying-In Hospital, and K. JEFFERSON THOMSON, M.D., Associate Physician, Metropolitan Life Insurance Sanatorium, Mount McGregor, N. Y.; Research Associate in Medicine, Albany Medical College, etc. With a Section Entitled "Delivery and Obstetrical After-Care of Cardiacs," by FREDERICK C. IRVING, M.D., F.A.C.S., Professor of Obstetrics, Harvard Medical School; Obstetrician in Chief, The Boston Lying-In Hospital. Pp. 402; 33 illustrations. Boston: Little, Brown & Co., 1941. Price, $5.00.

THE authors of this timely book very properly mention their considerable experience in the management of heart disease in young women. Of the three sections, the first deals with the diagnosis and treatment of pregnant women with heart disease; the second discusses the physiology of the circulation during pregnancy; the third describes the course of specific cardiovascular diseases throughout the childbearing age. Much is herein contained which could be found otherwise only by long personal experience and careful perusal of the periodical literature.

W. J.

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FRACTURES AND OTHER BONE AND JOINT INJURIES. By R. WATSON-JONES, B.Sc., M.Ch.Orth., F.R.C.S., Civilian Consultant in Orthopædic Surgery of the Royal Air Force, etc. Pp. 724; 1034 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, $13.50.

THE first edition of this work was published in January, 1939, and this second edition was published a year later. The first edition was written "in days of relative peace." Since then casualty surgery has become of such importance that the author has "rewritten the chapter on Open and Infected Fractures and War Wounds, and included recent developments in chemotherapy, blood and plasma transfusion, the treatment of wound shock, the closed plaster technique, and the technique of amputation."

The arrangement of this book is excellent and the illustrations are superb. The chapter on the Repair of Fractures, while short, is adequate and above all is clearly written so that even a student will not be confused

after reading it. The Reviewer is impressed with the repeated emphasis that is placed on adequate immobilization of fractured parts.

The sections on the treatment of open and infected wounds are well done. Exception will be taken by some to primary skin suture in any of the cases, even though chemotherapy is used as a prophylactic measure against infection. Fifteen grams of a sulfonamide seems a large amount to be utilized locally but others have used as much with very favorable results.

The final chapter deals with the organization of a Fracture Service and should prove very valuable in both civil and military practice. It is easy to understand why the first edition of this volume was exhausted before 12 months following its publication. The second edition will be equally well received for it is an unusually fine piece of work. I. R.

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SYNOPSIS OF DISEASES OF THE HEART AND ARTERIES. By GEORGE R. HERRMANN, M.S., M.D., PH.D., F.A.C.P., Professor of Medicine, University of Texas; Director of the Cardiovascular Service, John Sealy Hospital; Consultant in Vascular Diseases, U. S. Marine Hospital. Pp. 468; 91 illustrations. Second Edition. St. Louis: The C. V. Mosby Company, 1941. Price, $5.00.

THIS second edition is similar to the first in plan and content. By increasing the length by 124 pages, the author has been enabled to include a discussion of heart disease in relation to surgery and obstetrics, to enlarge the section on peripheral vascular diseases, and to add a chapter on military medicine. W. J.

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CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM Including the Cardiac Arrhythmias. By HAROLD E. B. PARDEE, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital; Consulting Cardiologist, Woman's and Methodist Hospitals; Attending Cardiologist, New York Polyclinic Medical School and Hospital. Pp. 434; 219 illustrations on 102 figures. Fourth Edition, revised. New York: Paul B. Hoeber, Inc., 1941. Price, $5.75.

THIS book continues to be a unique and concise guide for the student who wishes to learn both the fundamentals of the electrocardiographic method and abnormalities of the electrocardiogram which may be encountered in clinical medicine. According to the Preface: "Since the publication of the last edition of this book the use of precordial leads has added greatly to the diagnostic value of the electrocardiogram." The use of precordial leads is accordingly discussed and illustrated. W. J.

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BERKELEY MOYNIHAN, Surgeon. By DONALD BATEMAN. With a Preface by LORD MOYNIHAN. Pp. 354; illustrated. London: MacMillan & Co., Ltd., 1941. Price, $4.00.

DURING the past year several biographies and autobiographies of famous surgeons have been published. Among the great technical surgeons of our time Moynihan ranks near the top. This is a simple story of his life and Dr. Bateman has avoided the accusation of hero-worship. Moynihan, the man and the surgeon, lives again in this volume. His rise from poverty to wealth, from an assistant house surgeon to the greatest surgeon in Britain reads like a tale of Horatio Alger. The volume covers not only his British associations, but throughout one finds references to American colleagues and American surgery.

With all the honors that were bestowed upon him in Britain and in this country, he, like many other eminent men, failed to be made a Fellow of the Royal Society. It was a great blow. One by one nearly every honor had come to him, but this one, which he wished above all others, was denied him and he became a bitter man. It was an unfortunate thing that he finally attacked the President of the Royal Society in a letter to the *Times*.

Dr. Bateman in a remarkably able fashion sets forth this great man's virtues and faults, his generosity and his selfishness. It should be read by all surgeons, many internists and by all those who are interested in the biography of illustrious men. I. R.

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Orbital Tumors. By Walter E. Dandy. Pp. 168; 100 illustrations. New York: Oskar Piest, 1941. Price, $5.00.

This small book is a monograph in which the author presents his wide experience, covering a period of over 20 years, with orbital tumors. The material is presented in the form of 31 case reports accompanied by good photographs and excellent sketches.

In the summary and conclusions, the author stresses that 80% of the tumors involved both the orbit and the cranial cavity. This fact forms a logical basis for attacking these growths by the intracranial route. The operative procedure, identical with that used for hypophyseal tumors, is well described. The approach visualizes, at the same time, both the cranial and orbital contents and is the only one which allows removal of intracranial extensions and exact identification of the orbital structures.

This presentation of the types, pathology and management of orbital tumors should be of value to both the neurosurgeon and the ophthalmologist. It should make the latter wary of attempting removal, by the anterior or lateral approaches, of tumors lying deep in the orbit, or any in which there is suspicion of intracranial extension. A. C.

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Einführung in die Allgemeine Chirurgische Diagnostik. By Dr. G. Dardel, Privat-Dozent für Chirurgie, Bern. Pp. 86. Bern: Hans Huber, 1941. Price, Fr. 6.80.

This little paper-bound monograph was written for those young graduates who are beginning their surgical training. It represents the basis of a surgical diagnostic course which the author has given in Bern. He acknowledges the debt he owes to Theodor Kocher and Fritz de Quervain. It includes a great deal of material given in a very abbreviated form. However, it is a good little book and those who can read German fluently will find it useful and helpful. I. R.

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Essentials of Endocrinology. By Arthur Grollman, Ph.D., M.D., Associate Professor of Pharmacology and Experimental Therapeutics in the Medical School of The Johns Hopkins University. Pp. 480; 74 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, $6.00.

This book deals with the fundamentals of endocrinology in a simple, direct manner that should be useful for clinicians and medical students. There are excellent illustrations of gross and microscopic pathology. In spite of this, to the Reviewer, a pathologist, the descriptions in the text of the morphologic changes in disease show a lack of personal experience by the author in the field of pathology. For instance, most pathologists would not agree with the author's explanation of the renal changes in Addison's

disease, his reference to malignant tendencies of adrenal cortical adenomas and some of the descriptions of microscopic lesions in endocrine organs. However, the author, as physiologist and pharmacologist, has an opportunity of treating of those phases more authoritatively than usually can be done in books on endocrinology.

There is an interesting section in each chapter giving a brief historical account of the significant steps in the development of our knowledge of endocrine function and disease. A welcome feature is the absence of enthusiasm for irrational therapeutics so prevalent in many books on endocrinology.

This book will be found a useful source of information for all those who are not primarily endocrinologists. I. Z.

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Exercises in Electrocardiographic Interpretation. By Louis N. Katz, A.B., M.D., Director of Cardiovascular Research, Michael Reese Hospital, Chicago; Assistant Professor of Physiology, University of Chicago. Pp. 222; 128 illustrations, containing 189 electrocardiograms. Philadelphia: Lea & Febiger, 1941. Price, $5.00.

This atlas is designed to be used in connection with the author's current book entitled "Electrocardiography." It contains examples of the usual tracings to be encountered while reading clinical electrocardiograms, together with adequate explanatory material. A number of tracings labeled "definitely abnormal," might better have been described as "borderline or normal," in the Reviewer's opinion. W. J.

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## NEW BOOKS.

*Outlines of Industrial Medical Practice.* By Howard E. Collier, M.D. (Edin.), Ch.B., Formerly Reader in Industrial Hygiene and Medicine, University of Birmingham; Certifying Factory Surgeon, etc. Pp. 440. Baltimore: The Williams & Wilkins Company, 1941. Price, $5.00.

Medical Conferences of the University of Pennsylvania Bicentennial Celebration. *Development of Occlusion* (M-12). By William K. Gregory, B. Holly Broadbent and Milo Hellman. (Pp. 72; 49 illustrations. Price, $1.50.) *The Study of Man* (M-B). By Lawrence J. Henderson. (Pp. 22. Price, 25c.) Philadelphia: University of Pennsylvania Press, 1941.

*Infantile Paralysis.* A Symposium delivered at Vanderbilt University, April, 1941. Pp. 239; illustrated. New York: The National Foundation for Infantile Paralysis, Inc., 1941. Price, $1.25.

Clinical and Experimental Investigations on the *Genital Functions and their Hormonal Regulation.* By Bernhard Zondek. Pp. 264; 59 illustrations. Baltimore: The Williams & Wilkins Company, 1941. Price, $4.50.

*Papers of Wade Hampton Frost, M.D.* A Contribution to Epidemiological Method. Edited by Kenneth F. Maxcy, M.D. Pp. 628; illustrated. New York: The Commonwealth Fund, 1941. Price, $3.00.

*X-Ray Therapy of Chronic Arthritis* (Including the X-Ray Diagnosis of the Disease). Preliminary report based on 100 patients treated at Quincy, Illinois. By Karl Goldhamer, M.D., Associate Roentgenologist, St. Mary's Hospital and Quincy X-Ray and Radium Laboratories, etc. With a Foreword by Harold Swanberg, B.S., M.D., F.A.C.P., Roentgenologist, St. Mary's and Blessing Hospitals, etc. Pp. 131; 24 original illustrations by author, 2 roentgenograms, and 4 tables. Quincy, Illinois: Radiologic Review Publishing Company, 1941. Price, $2.00.

*Medical Progress Annual 1940.* A Series of Fifty-two Reports Published During 1940 in the New England Journal of Medicine. Managing Editor: ROBERT N. NYE, M.D. Pp. 625. Springfield, Ill.: Charles C Thomas, 1941. Price, $4.00.

*Exercises in Electrocardiographic Interpretation.* By LOUIS N. KATZ, A.B., M.D., Director of Cardiovascular Research, Michael Reese Hospital, Chicago; Assistant Professor of Physiology, University of Chicago. Pp. 222; 128 engravings containing 189 electrocardiograms. Philadelphia: Lea & Febiger, 1941. Price, $5.00. (Review, p. 445.)

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# PROGRESS
OF
# MEDICAL SCIENCE

## PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF
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### ALLERGY AND RESISTANCE TO INFECTION.

IN 1891 Koch described the phenomenon which has since been known by his name. When tuberculous guinea-pigs are reinoculated intracutaneously 4 to 6 weeks after the primary infection there is an intense inflammatory reaction within a few hours, followed by ulceration and ultimately healing without involvement of the regional lymph nodes. Von Pirquet, in 1906, proposed the term "allergy" for this altered response of tuberculous tissue to reinfection. The localizing effect of acute inflammation was already known, and it was natural that the accelerated, intensified inflammation of allergy should be identified with resistance to reinfection (Römer[46]). In more recent years Krause, Zinsser, Opie and many others have more or less completely related immunity in tuberculosis to the allergic state. Zinsser, Ward and Jennings[59] concluded in 1925 "the artificial production of allergy by dead bacilli or other products appears a hopeful direction for the investigation of immunization in tuberculosis." The concept was extended to infection in general. Probably the most widely quoted opinion in contemporary discussion is due to Opie,[36b] "Both with anaphylactic inflammation and with the inflammatory reaction of infected animals, vital organs are protected at the expense of local injury."

During the last decade the dissenting voices of Rich and his associates have been largely responsible for the increasing doubts cast on the allergic reaction as a mechanism whereby invading bacteria are localized or destroyed. It is to be suspected that their cogent arguments have modified some of the opposing views. In 1936, for example, Opie[36c] wrote: "In the process of local fixation it is not possible to estimate the relative importance of antibodies, of phagocytes and of the inflammatory reaction itself." Rich feels that the factors which govern resistance to infection are quite separate and distinct from those concerned in allergic inflammation even though both attributes result from

the same exposure. This does not imply that hypersensitivity does not modify the operation of immunity. Indeed Rich and McCordock,[43] in 1929, pointed out that increased transudation from the blood-vessels must, by dilution, help to neutralize the injurious effects of the products of bacterial disintegration in the hypersensitive body. The same process clearly makes available to the tissues whatever factors of protection circulate in the blood. Conversely, those very products of bacterial disintegration, in comparable concentration, would not cause necrosis of normal non-sensitized tissue.

Many of the earlier writings concerning the relation between allergy and immunity dealt with the events which follow parenteral introduction into an animal of heterologous protein. The identity of the "immune body" responsible for anaphylactic sensitization and for the various *in vitro* "immunity" tests was established, and it became a commonplace not only to state that hypersensitivity is a stage in the development of immunity, but to transfer the reasoning from inert molecular protein to bacterial allergy, and resistance to living self-propagating infective agents. The correlation may exist in respect of these bacterial components which behave after the fashion of heterologous proteins, that is, yield humoral antibodies, passively sensitize the guinea-pig uterus, and exhibit an immediate hypersensitive response.

**The Nature of the Hypersensitive State.** Microörganisms are complex chemical entities. During infection the tissues may become sensitized both to polysaccharide and protein. There is overwhelming evidence that the delayed tuberculin type of hypersensitivity due to the protein of microörganisms is unaccompanied by humoral antibody, and cannot be passively transferred to normal animals. It is achieved only by the introduction of intact bacteria, alive or dead. Hypersensitivity produced by the injection of bacterial proteins conforms to the anaphylactic type, and while the tissues react violently and immediately to that protein, they will not react hypersensitively to the injection of the intact bacteria (Baldwin;[2] Bouquet, Sandor and Schaefer;[5] Rich;[40b] Sabin and Joyner[49]). As Rich[40c] pointed out in 1941, this type of experiment has no relation to bacterial allergy, in which condition an antibody mechanism is predicated only on the specificity of the reaction and the fact of desensitization.

The hypersensitivity is a property of the individual cell. Holst[23] and Stewart and coworkers[52] showed that the addition of tuberculin to leukocytes from animals hypersensitive to it kills the cells. Rich and Lewis,[42] using the tissue culture technique, showed that cells from the blood and fixed tissues of tubercular animals were distinctly more susceptible to the toxic action of tuberculin than were normal cells. Aronson[1a] and Moen and Swift[34] confirmed these findings and found that the sensitivity persisted through several transplants. They suggested, therefore, that this "represented a more or less permanent acquired characteristic impressed on the cell as a result of the infection." Moen[33] later showed a similar effect in cultures of mononuclear cells obtained from the pleural cavities of tuberculous animals and found the tuberculin sensitivity to extend through three transplants over a period of 29 days. This raises the question of how valuable is the increased phagocytic capacity of mononuclears derived from actively

tuberculous or vaccinated guinea-pigs for tubercle bacilli, as Lurie[27b] found. This cellular hypersensitivity must mitigate against survival of the phagocytic cells. That phagocytosis may aid in the dissemination of microörganisms was beautifully reëmphasized by Goodpasture and Anderson[20] in the living tissues of the chick embryo.

By contrast, the allergy which develops to bacterial polysaccharide is of the immediate anaphylactic type, and usually is accompanied by circulating antibody (Harley[21]). The correlation between allergy and antibody is less exact in normal persons (Tillett and Francis;[54] Finland and Sutliff[15]) due possibly to difficulties in titrating small amounts of the antibody and to the well-known inverse relationship between anaphylactic sensitivity of the tissues and blood antibody. In this type of sensitivity the individual cells in tissue culture are not affected by the addition of the specific antigen (Aronson[1b]). This is in agreement with the views of Opie that local anaphylaxis depends on a precipitin reaction and serves to fix the antigen within the tissue spaces. That type-specific antibody, without the intervention of inflammation, likewise fixes the pneumococcus, was shown by Rich and McKee.[44] Nevertheless, the rapid inflammatory response may serve to support the mechanism of resistance, even though it is not the prime factor, by facilitating access to the tissue spaces of antibody and phagocyte. Freund[17] and Douglas and Simpson[12] concluded that antibody permeates the fluids of the uninflamed tissues everywhere. McMaster and Parsons,[30] on the other hand, do not believe extracellular fluid exists in mammals under normal circumstances, but Maurer[31] succeeded in collecting from the extracellular spaces of frog muscle a clear fluid which had a protein content of 1.53% as compared with a serum protein of 4.23% from the same animals. Frogs and mammals differ markedly in the permeability of vessel walls, and it may be recalled that Krogh, Landis and Turner[25] considered the filtrate from human capillaries to contain less than 0.1% of protein. Thoracic duct lymph is this filtrate usually concentrated by absorption of water and salts. At any rate, the possibility exists that antibody globulin may be present in the blood and tissue spaces in markedly different concentration. The increased capillary permeability which follows even trivial damage to the tissue (Rous and Smith[48]) must tend towards equalization of the two concentrations. Indeed, Lurie[27b] found that typhoid agglutinins collected in the pleural cavity of tuberculous guinea-pigs as a result of a chemically induced inflammation to a concentration higher than that in the blood. Mention must be made, too, of the work of Dienes[10] who considers that the early stages of specific immunity are associated with absence of circulating antibody and a delayed tuberculin type of reactivity. McBroom and Schlesinger[28] obtained similar evidence. It is difficult to say how far this reconciles the differences between protein and polysaccharide sensitivities.

The tissue response in allergic inflammation does not differ qualitatively from that due to acute inflammation produced by any irritant in the normal body. The vascular and cellular changes are identical. Dienes and Mallory[11] considered that in hypersensitive inflammation mononuclear cells predominate in the exudate from the beginning. Most observers, however, agree that the normal sequence of polynuclear,

mononuclear cells is followed. The actual physiologic stimulus which determines these changes is the liberation of histamine and the substance discovered and named leukotaxine by Menkin.

Finally, as far as generalizations can be drawn from infections of different types, the problem under discussion is this. The immune animal potentially possesses phagocytic and antibody mechanisms of resistance, and two conditions of hypersensitivity by which specific inflammation can be provoked. Are these latter essential or beneficial to the animal in its efforts to combat infection?

**Does Allergic Inflammation Localize Infection?** The path of absorption of chemical substances from the tissues depends on the size of their molecules; the smaller molecules are absorbed by the blood stream, the larger by the lymphatics (Drinker and Field[13]). It was shown many years ago (Noetzel[35]) that bacteria travel from the tissues by the lymphatics rather than the blood stream. Barnes and Trueta[3] showed that bacteria placed in freshly made wounds could be found only in the lymphatics. This agrees with the observation of McMaster and Hudack,[29] that in freshly made wounds the blood-vessels shut down and thrombose within a few minutes of the injury, while the lymph-vessels remained patent for over 48 hours.

Since the observations of Issaeff in 1894 it has never been questioned that well-established inflammation forms a mechanical barrier which limits the dissemination of bacteria and other particulate matter, with a few exceptions, depending on the variety and virulence of the organism (Cannon and Hartley;[7] Clark[8]). The effect was ascribed to a wall of macrophages by Gay and Morrison,[19] to neutrophils by Clark.[8] Opie[36a] showed that in local anaphylactic inflammation the small blood-vessels and lymphatics are injured and often undergo thrombosis. Menkin in an extended series of papers has emphasized the importance of this lymphatic blockage in localizing infection.

When bacteria, however, are introduced into the normal tissues of an animal, dissemination may take place before sealing of the lymphatics or mobilization of leukocytes can occur. Rivers and Tillett[45] found that a mild inflammatory irritant such as beef broth injected into the skin of rabbits protected against streptococci injected 24 hours later, but did not protect when organism and irritant were injected together. This was confirmed by Rich[40a] and Menkin himself[32a] found that for the localization of ferric chloride or colloidal iron in a chemically inflamed area the irritant must be injected some time previously. In some cases the spread of bacteria was hastened.

The immediate fate of microörganisms which gain access to the tissues is determined by the dynamics of capillary and lymphatic function in the early stages of inflammation. As far as the vascular bed is concerned, the main changes are vasodilatation with an increase in capillary pressure and permeability. These are responsible for the increased capillary filtration, and for the parallel increase in lymph flow and pressure (Field, Drinker and White;[14] Barnes and Trueta[3]). There seems no reason to doubt that edema and increased lymph flow *per se* facilitate dissemination (Rhoads and Goodner;[39] Rich and McKee;[44] Lurie[27a]). After an interval of time, and one school of thought (as logic demands) has endeavored to show how short this important interval may be,

the lymphatics become occluded by fibrin thrombi. Menkin considers that retention of materials in an acutely inflamed area depends on the fibrin network formed in the edematous tissue spaces or in lymphatic vessels. He showed, moreover, that the rapidity with which bacteria are walled off by this process is a function of the intensity of the injury they cause, and this in turn varies with the nature of the microörganism. For example, *Staph. aureus* introduced locally induces lymphatic blockage within an hour, whereas after cutaneous inoculation of hemolytic streptococci the lymph channels are open as long as 2 days. These events appear to be related, not to the plasma coagulase effect of the one and the fibrinolytic effect of the other, but to the degree of tissue damage. It is perhaps significant that Lurie[27a] found on introducing melted agar impregnated with tubercle bacilli and trypan blue subcutaneously into normal and highly immunized rabbits, the early rush of lymph from the focus of reinfection was so intense that both bacilli and dye were swept over to the draining lymph nodes much more rapidly in the sensitized than in the normal animal. He stated,[27b] "However, one cannot conclude from this that in man also the exaggerated inflammation aids rather than hinders the dissemination of the bacilli of reinfection. Rabbits become only moderately sensitized to the tubercle bacillus, as compared to the exquisite sensitivity that man acquires as a result of a tuberculous infection." Lurie therefore repeated the experiment on guinea-pigs and found that the bacilli of reinfection are more effectively fixed at the portal of entry in a sensitized and immunized pig than in a comparable rabbit. This he correlated with the greater degree of injury in the guinea-pig, the more abundant exudate and a histologic demonstration of the more rapid thrombosis of the adjoining lymph-vessels to give a clot with a finer sieve formation than does the rabbit. The correlation was clouded somewhat by finding that the human gave a clot histologically of the rabbit type. Thus, Menkin and Lurie demand an intense degree of inflammation for localization, and admit that minor degrees may aid dissemination. This contrasts with the views of other protagonists of the allergic theory. Wilson *et al.*,[58] for example, find that a mild degree of inflammation assisted their guinea-pigs to resist tuberculous reinfection: a high degree "was worse than no allergy at all."

What bearing does this have on the inflammation of allergy? Rich pointed out in 1930 that the deposition of bacteria in an area that is *already inflamed* when the bacteria are introduced is not comparable with what occurs in a hypersensitive reaction, when the inflammatory reaction must develop after they reach the tissues. Bacteria have long been known to spread with great rapidity from the portal of entry in the normal animal. Noetzel, for example, in 1906 found bacteria in the regional lymph glands 5 to 10 minutes after they were injected into the knee joints of rabbits. Rich and McKee stated in 1934 that "since the time required for an effective amount of inflammation to appear about invasive bacteria, even in the allergic body in which the process is accelerated, has been found by all who have investigated the matter to be distinctly longer than the time required for bacteria to spread from the site at which they lodge." Rich had shown experimentally in 1930 that the injection of a mixture of two bacteria into

an animal hypersensitive to one of them, even though it reproduced the time conditions of an accelerated hypersensitive inflammation in the previously normal tissues, the spread of the bacteria to which the animal was not immune was accelerated rather than retarded. Cannon and Hartley[7] and others confirmed this failure of allergic inflammation to protect rabbits against pneumococcal infection. Rich and McKee[43] concluded that the primary localization is accomplished by the immune antibody, which acts to hold the bacteria at the site until the leukocytes can emigrate to attack and destroy them. After producing with benzol a leukopenia in immunized rabbits, they found that virulent Type I pneumococci, introduced intracutaneously, proliferate, but adhere to each other and to the tissues as well for hours after the controls have died with septicemia, even in the absence of microscopically detectable inflammatory exudate or thrombosis of lymphatics. In the absence of the leukocytes growth of the pneumococci proceeded to form large agglutinated masses in the tissues, until they penetrated the blood stream and the animal died with septicemia, even though its plasma was capable of passively protecting non-immune animals possessing leukocytes.

It has already been pointed out that allergic inflammation may be associated with a faster or slower rate of spread of tubercle bacilli than in normal controls.

**Does Allergic Inflammation Prevent Proliferation?** Many of the recorded observations either indicate that inflammation is not required, or fail to distinguish events occurring in an allergic animal from events due to the allergic state.

The numerous papers of Rich and his associates testify that in pneumococcus immunity localization and destruction of the bacteria are carried out by antibodies and phagocytes. The work has been amply confirmed (Rich[40c]). That hypersensitivity adds nothing to this effective immunity is indicated by Rich and Brown.[41] They showed that if the serum of animals that are hypersensitive and immune to the pneumococcus is injected intravenously into normal animals, the immunity is transferred but not the sensitivity.

Lurie[27b] reported quantitative determinations of surviving and metastasizing tubercle bacilli introduced into normal and sensitized (B.C.G.) guinea-pigs and rabbits. He found marked inhibition in the multiplication of the organisms in the cell-free body fluids, and noted without comment the numerous unsuccessful attempts to demonstrate *in vitro* bactericidal properties of serum derived from animals immunized against tuberculosis. Freund and Angevine[18] in rabbits pretreated with heat-killed tubercle bacilli intracutaneously concluded that virulent tubercle bacilli introduced by the same route multiply actively at the site of injection during the period of retarded lymphatic dissemination, and that the retardation is caused by local fixation and not by destruction of the organisms. The conclusion was correct in the sense that ample numbers of bacteria were present locally for spread to occur if the channels were open, but their figures show pretty well as much interference with local multiplication as with dissemination in the immunized animals. It will be recalled that Lurie[27a] found sensitization of the rabbit to promote lymphatic spread.

**Immunity and Allergy as Independent Variables.** The spontaneous waning of tuberculin sensitivity with persistence of acquired immunity suggests their independence. Willis[56] disagreed with this view in contending that reinfection caused hypersensitivity (and therefore resistance) to reappear in a shorter time than in non-immune controls. Schwabacher and Wilson,[50] and Wells and Brooke[55] found, on the contrary, that the development of hypersensitivity was delayed following reinfection. Freund and Angevine[18] raised a further criticism, which might be levelled at many other studies, of Birkhaug's[4] conclusion, that desensitization assists the resistance to reinfection, because Birkhaug did not show his animals to be desensitized both to tuberculin and living tubercle bacilli.

A varying ratio of the two components, hypersensitivity and resistance, to infection has been shown to depend on the route of immunization. Petroff, Branch and Jennings,[37] and Branch and Cuff[6] found that intravenous immunization with killed tubercle bacilli rarely induced tuberculin sensitiveness, whereas subcutaneous inoculation, for instance, established the same degree of immunity as well as hypersensitivity. Swift and Derick[53] similarly dissociated allergy and resistance, using streptococci. Many workers have stressed the efficacy of intracutaneous inoculation in inducing hypersensitiveness (Julianelle,[24] McBroom and Schlesinger[28]). Dienes and Schlesinger and McBroom, however, return to an earlier viewpoint and believe that allergy so induced is not only in part responsible for the early stages of the immune state, but that the early phase represents a tissue immunity in which fully developed resistance is associated with humoral antibody. It is difficult to fit this concept in with the experimental characteristics of the tuberculin type of sensitivity.

There is no need to review again the impressive testimony that desensitization experimentally, and maybe clinically, can abolish hypersensitivity and leave resistance intact. Rich[40c] gives an excellent bibliography. Those who feel that allergy is unrelated to immunity accept these experiments at face value: their critics find plenty to criticize. Freund and Angevine[18] would not accept tuberculin desensitization as proof of desensitization to intact bacteria. They feel that the large number of deaths in prolonged desensitization of vaccinated animals invalidated the experiments of Rothschild *et al.*[47] It seems natural that continued administration of large amounts of tuberculin over a period of months should impair the health of well or sick animals. In this respect Willis and Woodruff[57] suggested that the inanition, emaciation, and ulcers of the skin which followed daily injections of large doses of tuberculin may all be factors in bringing about the difference between the amount of tuberculosis in the desensitized and untreated animals. In a surprising pair of papers Wilson and his associates[58] state at the outset a disagreement with Rich's view that allergy plays no part in immunity. Their experiments on desensitization support Rich in entirety, the desensitized animals survived longer and had fewer lesions postmortem than allergic non-desensitized animals. Their discussion is a reconciliation of experiment and conclusion. They found a relation between the degree of sensitivity to tuberculin at the time of reinfection and survival time, and suggested that "(1) a slight

to moderate degree of allergy at the time of infection is favourable to survival, (2) a high degree of allergy is definitely unfavourable, (3) a very high degree of allergy is worse than no allergy at all." With less conviction and somewhat paradoxically they concluded that the higher the degree of sensitivity to tuberculin reached *after* injection, the longer the survival time. How this affects the fate of surviving bacteria is not clarified. Anent the question of desensitizing doses of tuberculin, they raise again the question of their immunizing value, in spite of numerous studies to the contrary, and despite the fact that, as Rich points out, it is the question of the hypersensitive state which is at stake. Tangentially, they then question whether desensitization is complete anyway, and suggest that repeated injection may maintain minor inflammatory reactions around each tuberculous focus in the body, with the result that the dissemination of the bacilli is retarded, and the rapid caseation which seems more liable to occur in the highly allergic animal is prevented.

**The Effect on the Lesions.** In tuberculosis, tubercle formation is incited by the lipoid fraction of the bacillus. Through the tissue culture studies mentioned above it has become clear that necrosis in these tubercles is the result of contact of hypersensitive cells with tuberculo-protein. The vascular changes accompanying inflammation are not essential to the process of caseation. Quantitatively it is likely that the amount of tuberculo-protein necessary will vary with the degree of hypersensitivity of the individual cells, and in general will require some multiplication of the bacteria if the numbers which gain access to a given site is small. A given number of bacteria will do less damage in a normal than in a hypersensitive body, and their effect can be minimized by desensitization (Rothschild;[47] Wilson[58]). Wilson and coworkers believe desensitized animals live longer than controls and show less severe lesions because in the controls "allergy has been allowed to develop to a point at which the very intensity of the reaction in the internal organs—particularly the lungs—proves prejudicial to life." Freund and Angevine[18] believe that the allergic reaction in the skin of intracutaneously inoculated animals protects the rest of the body. They state, however, "it is conceivable that allergic reaction in internal organs also promotes the formation of tubercles and development of caseous necrosis." Manifestly all shades of opinion dislike marked allergic inflammation in the viscera. Henrici[22] correctly emphasized the importance of considering the site of the allergic reaction. In the Koch phenomenon the organisms and the products of the reaction are cast off to the exterior: when the same reaction occurs in the lung or kidney it may result in an extension of the disease.

Coccidioidal granuloma is the reinfection form of San Joaquin "valley fever" or "desert fever," appearing after the skin tests are positive. The mortality in primary infection is virtually *nil*, in the reinfection type about 50% (Dickson and Gifford[9]). However, only 1 in 354 cases of "valley fever" goes on to granuloma. Henrici suggests that in all the deep-seated mycoses the progressive course and lesions are dependent on the state of hypersensitiveness which develops in the patient. He points out, too, that in the dermatomycoses the ultimate healing of the lesion is due to the allergic state.

Opportunity for exposure and sensitization increases with age, and reasonably contributes to the age differences in both the acute and chronic disease, particularly if the portal of entry is the respiratory tract. Lauche[26] pointed out that lobar pneumonia, which is rare in young infants, may occur in the first few days of life, and increasingly frequently as infancy is passed. Lauche regards lobar pneumonia as the response of an allergic body having a partial immunity to the infecting type of organism, the sensitization of the infants being passively transferred *in utero*, the adult being sensitized as a result of minor upper respiratory infections. According to this view, allergy to the pneumococcus does play a part in the development of lobar pneumonia. Sharp and Blake[51] and others provided experimental support for this contention. Reimann[38] suggests that the tendency for recurrence of lobar pneumonia in the same individual is due to persistence of this allergic state. Recurrences have the same type distribution as first infections (Finland and Winkler[16]) but the incidence of bacteriemia and the case fatality rate seems generally lower. One explanation of this paradox of increased susceptibility and greater resistance is that the one depends on nucleoprotein sensitization and the other on antipolysaccharide antibody. Opie[36c] considered that while allergy was not essential in the production of diseases like lobar pneumonia, rheumatic fever, glomerulonephritis, it may modify their course.

**Conclusion.** The burden of proof appears to be with those who believe that hypersensitive inflammation is an important mechanism in resistance to infection. Moreover, in chronic disease like tuberculosis, the tissue destruction is a manifestation of allergy. This is not to deny the value of vaccines or first infection as an immunizing experience, nor is it necessary to debate the merits of these procedures.

The mechanisms of resistance differ widely in respect of different infective agents, and in some diseases like tuberculosis there exists no clear basis for the state of resistance. It would seem logical to conclude that allergic phenomena would differ vastly, therefore, in importance, in diseases like diphtheria, pneumococcal infection and tuberculosis.

In Gay's textbook of 1935, *Agents of Disease and Host Resistance*, the Seegals divided infections into three categories: those in which allergy played no part in resistance, those in which allergy assists resistance and those in which it handicaps resistance. This opinion, to which Rich subscribes, is probably nearer the truth than the extremists of either school in the controversy.

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## PREVENTIVE MEDICINE AND EPIDEMIOLOGY.

UNDER THE CHARGE OF

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### CONSTITUTIONAL TYPES AND SUSCEPTIBILITY TO PARALYSIS IN POLIOMYELITIS.

Even in the earliest writings about poliomyelitis, there is found the suggestion that the paralytic disease exhibits a tendency to selective occurrence in certain types of individuals. The first account of what is clearly poliomyelitis is believed to be Underwood's description in

1799,[27] in which he remarks, "I have seen it in others who are older, and the finest children." Similar notations are found in the observations of other clinicians during the 19th century. Shaw (1823), ". . . . strong and healthy children are more frequently affected than those of a weakly constitution." Heine (1840), "Before the illness there had been complete health and well-being, and a strong and blooming bodily constitution." Sinkler (1875),[23] "The affection usually occurs in a strong, healthy child between 6 months and $2\frac{1}{2}$ years of age. . . . J. R. L., age 4 years, was brought to my clinic November 18, 1874. . . . Is a robust, healthy looking boy, with light hair, blue eyes and sound teeth. . . . The excellent state of the general health in this affection is very striking . . . . Almost all of the children who are brought to our clinic suffering from infantile palsy are remarkable for their fine, healthy appearance." Caverly (1896):[8] "Case 1. Boy 3 years; previous health good; active child; stronger than his brother 2 years older. Case 2. Boy, $3\frac{1}{2}$ years; sturdy child; most active of a family of 3 children. . . . Of the 46 cases in which the previous health of the sufferer is given, in 35 it is good and in 11 it is poor. It is quite certain that the strong, healthy children preponderated." Madison Taylor (1898):[19] "A. C., age 12, was a perfectly vigorous boy until a fortnight previous. . . . D. B., age 4, a fine vigorous boy, the first child of young, handsome parents. . . . R. P., a robust boy 2 years and 5 months. . . . G. S., a healthy girl of 10 years and 6 months." Hill (1909):[16] "As a general rule, the children affected had been exceptionally robust and active, with good appetites and living on a general diet." Wickman (1913):[28] "Heine-Medin's disease usually attacks those in perfect health."

Such exclamatory comments concerning children attacked by paralytic poliomyelitis, appearing in studies of the disease before the virus and its mode of spread became the center of attention, are enough to indicate that whatever individual predisposition there may be, it does not reside in being "run-down" in the ordinary sense of the word. There is tacit agreement today among many clinicians with the ideas expressed by these earlier students as shown, for example, by their frequent reaction to the epidemiologic evidence that individual susceptibility to paralysis is a major determinant. Many physicians, and even laymen, when it is suggested that among the many exposed to the virus only the few susceptibles are paralyzed, insist that they are not "run-down;" the general assumption being that susceptibility to infection is the result of a "run-down" condition in the ordinary sense—undersize, underweight, undernourished, and the like. Thelander and Pryor[26] have stated, "Our observations bear out those of others that it is not the delicate, handicapped child that is most frequently the victim of poliomyelitis, but just as often the most sturdy. That some of our choicest and handsomest children are endocrine anomalies, . . . . however, is not borne out by our studies" (anthropometric).

But in earlier times, these ideas did not take root as a fundamental epidemiologic feature of the disease. The demonstration of its infectious nature, the isolation of the virus, and the experimental transmission of the disease had, by 1916, shifted emphasis to the mode of spread as the important epidemiologic determinant. Although much evidence had accumulated that dissemination of the virus is widespread and

that abortive cases or healthy carriers play the major rôle (Wickman, Caverly, Flexner and his co-workers), paralysis occurring only in the minority of those exposed, the reasons were sought in parasitic and environmental rather than host factors.

In the flush of this period of bacteriologic observations, during the 1916 epidemic, Draper[9a] broke away from conventional trends with the following clinical observation.

"The patients displayed certain definite morphologic characteristics which appeared with insistent regularity. The type of child which seems most susceptible to the disease is the large, well-grown, plump individual who has certain definite characteristics of face and jaws; is broad browed and broad and round of face. The teeth are particularly interesting. It was noted that in 50 to 60 per cent of all the cases in the hospital at Locust Valley, the central incisor teeth of the upper jaw were separated by a cleft of varying width. The wide-spaced dentition has been a striking feature and frequently involves all the single teeth of both jaws, so that each tooth stands entirely free."

"Among the adolescents and young adults who acquired poliomyelitis and in whom the disease seemed always to be most severe and, indeed, usually fatal, the type differed from that just described. Instead of the very large, well-nourished individuals with widely spaced teeth, there appeared a more delicately made type. Of the 6 or 8 fatal cases in young adults, seen by the writer, the similarity of appearance of the individuals was so striking that all might have been of one family. All were brunettes, with very delicate dark skins and high coloring of cheeks and lips. Often small, deeply pigmented moles were present on face or neck. There was in every case a definite though finely chiseled maxillary prognathism, and instead of dental separations a tendency to crowding of the teeth. This type was so definitely associated with the severe form of the disease that we have come to attach grave prognostic significance to it. In this connection, it is interesting to note that a surprising number of the fathers of children ill with poliomyelitis presented striking anthropologic markings. Thus one was a definite acromegalic, while two others were clearly Froehlich types, dark-haired, fat faces and bodies, narrow shoulders, broad hips and knock-knees. In three others, maxillary prognathism was marked, and although the body stature was small the hands were very large and broad, and there was great physical strength. A seventh father had widely separated upper incisor teeth and was a tall, big-boned individual. Four of the mothers in this group had moderate or marked exophthalmos and were high strung, intensely nervous women. In another instance, the mother of two desperately ill cases had an unusual degree of maxillary prognathism."

"Whether or not these facts have a bearing on the question of susceptibility is still problematical. The cited examples, however, are merely a few of the very many similar observations made throughout the summer by the diagnosticians of the New York State Department of Health on Long Island. It is interesting, too, to record the numerous instances of 2, 3, 4 and 5 cases in families with such parental types, suggesting possibly a true family susceptibility."

In a later paper, Draper[9b] stated: "The foregoing observations

gave impulse to investigate the general topic of human constitution in relation to disease. The point of view in regard to this matter and the technical methods which have been developed during the intervening years have been applied to cases arising in the epidemic which has just drawn to a close (1931)."

"Some of the morphologic characters of this group of people which differ from the general population can be demonstrated by anthropometry and expressed in numerical values. Other features cannot be subjected to mensuration. But observational and descriptive methods suffice to display the striking qualities. The interpupillary space is unusually wide. This feature is not only emphasized in relation with the upper face (nasion-prosthion) but likewise with the facial diameter, although the latter is also unusually wide. These characteristics, in addition to the somewhat greater distance between the inner canthi, give to the face of these children the broad, wide-eyed expression which was previously noted. In almost all cases there is a definite overbite and frequently a noticeable or pronounced maxillary prognathism. The gonial angle formed by the ascending and horizontal rami is more obtuse in the subject of infantile paralysis than in the members of the control series of miscellaneous diseases. This character is similar to that found in adults of the so-called asthenic variety, as for example, members of the peptic ulcer group who display a rapidly exhaustible energy capacity (adrenal). The narrow subcostal angle is likewise characteristic of these. In this series the inner border of the scapula was not more frequently concave than in the controls. It is interesting to note that, in paradoxical association with these evidences of the gracile form, the subjects of acute anterior poliomyelitis tend to gain weight and are often definitely pudgy, fat types. The hand index (breadth-length ratio) shows a short, broad form. This is ordinarily correlated with acromegaloid trends in the facial structure. So far as the rest of the body is concerned, the one outstanding measurable character is the biiliac-biacromial diameter ratio. The pelvis of these individuals is definitely wide as compared with the shoulders. This character is generally accepted as a definite mark of the neuter or feministic type. In both sexes it marks that deficient gonad activity which results in retarded development, and checks metamorphosis toward the finished form of the mature individual of either sex. While this characteristic is usually associated with curving body contour and feminine fat deposits, there are certain individuals afflicted with infantile paralysis who differ. These, on the contrary, are long, lanky, and often possess exceedingly large long-boned hands. Certain of the young male adults are of this type. As might be expected in the individuals with feminine contours and increased fat, the external genitalia are small; the penis less than average size with pointed glans. The scrotal sac is short. Several cases of unilateral cryptorchidism appeared, and numerous instances of short spermatic chord which resulted in a partial cryptorchidism on contraction of the cremaster muscles. Before puberty the rotund contours of the male children resemble those of females. But there are no especially striking physical proportion aspects of the adolescent girls or adult women. Comparatively few of these, however, are stricken."

It is evident that Draper encompassed more than dimensions in his concept of the type of individual which he regarded as susceptible to paralysis. Thus, he writes:[9c]

"If perhaps homo sapiens had spent a fraction of the energy in the effort to explain himself as he has poured through his intellect upon the rocks, the trees and other animals, he would doubtless be wiser even than he is today. But it is only within the last quarter-century that he began rationally to face the humiliating realization that an adverse environment is not the sole cause of such troubles as may befall him."

"Medicine focussed on sick spots in organisms which were partially or totally out of commission. Somewhere back in 1912 or so, Dr. Jelliffe passed the notion on to me in one of his flaming utterances. And, subsequently, it has always been an honest gratification to me when, on occasion, I've handed the ideas back to him dressed in anthropometric clothing or gossamer philosophic veils and he has accepted them for publication in his journal."

"I have often wondered why it was that the psychiatric branch of medicine was more receptive to and sought more eagerly than the others to understand the creature man; why the psychiatrists before the others strove to capture that quality which Samuel Butler called 'personal identity' and D. H. Lawrence simply 'otherness.' Perhaps the fascination of watching the wheels go around in reality, the respiratory rhythm, the passage of a nerve impulse, the amazing and subtle electropotential flowing from cardiac systole, explains our delinquency. Perhaps the mechanisms trapped the internist's imagination and surely any one of them would suffice. . . . But, you cannot study the heart's function by itself and hope to comprehend the creature man. Furthermore, the internist has been forced to give immediate relief for suffering. He inevitably must focus upon an ailing area or organ. The psychiatrist, on the other hand, from the time of his interneship has ever faced the whole person in action: how does he look? what does he do? what sort of creature can he be? Such questions by virtue of their social implications encourage the notion of personal identity or otherness."

"For the internist to be powerfully impressed by this last named quality of a human being, a large epidemic is almost essential. The clinical observer of such a calamity cannot fail to perceive that stricken persons are of quite a different stripe from those who remain well"—simply another way of saying that stronger impressions come from seeing large numbers of cases within a sufficiently short space of time to enable one to visualize them as a group.

Draper and Dupertuis[10] continued studies of the evaluation of constitutional characters of paralyzed persons over a period of years. The method used for studying the external morphology was composed of mensuration, observation and statistical analysis. The findings indicate that persons susceptible to the virus of acute poliomyelitis possess a special constitutional type of morphology which differs significantly from that of non-susceptibles. Variations occur in the degree of morphological differences, extending from those imperceptible to those of high statistical significance. Among susceptibles, there is a lack of coördination between growth and development which is expressed in a tendency to overgrowth and retarded development.

The peculiar presence of the Mongoloid eye and the fetal and infant-like retardation of the eye-nose zone suggest adverse genetic or intrauterine forces. The person susceptible to infantile paralysis is a different and in some way incomplete phenotype.

These morphological observations were analyzed by statistical methods and the original findings largely substantiated. According to the indices used by these investigators, paralyzed individuals showed a higher percentage of a greater number of the pertinent characters than the normal. They point out, however, that human morphology is significant only insofar as it correlates with other characters of the total personality.

Dissenting views of Draper's thesis have been taken by Levine, Neal and Park,[18] and also by Thelander and Pryor.[26] The former investigators used relatively few measurements, no one of which showed a difference; and the average age of their patients was 4.5 years, whereas in the studies reported by Draper the mean age was 9 years. Thelander and Pryor, using a number of anthropometric indices, could find no demonstrable differences in anatomical characteristics between 100 children paralyzed from poliomyelitis and 518 normal controls of the same age and sex. It is not clear from their paper that some of the measurements were not influenced by effects of the disease. For example, patients with atrophy of one or both shoulders were apparently included in their series of biacromial diameter observations.

Draper has always taken into account the whole individual, stating, "Afflicted children have something about their appearance and form and expression definitely absent in those who escape. . . . It would seem that the paralyzed child possesses the same essential otherness in susceptibility as does the necessary virus,"[9c] while in the two studies cited which differ from his thesis, the observations have been confined to measurable dimensions, no one of which considered separately would necessarily be a measure of susceptibility. Thelander and Pryor have said, either facetiously or naively, "That variations in susceptibility exist cannot be denied, but that these variations in susceptibility to an ultramicroscopic organism can be measured by centimeters and grams in a highly complex physicochemical and electrodynamic nature, such as the human body with heredity linked to chromosomes, genes and protones, does not necessarily follow."

Epidemiologically, there are indications which point to differences in the exposed, rather than differences in exposure, as determining the occurrence of paralytic poliomyelitis. Expressions of the widespread and more or less uniform dissemination of the virus are seen in such features of the clinical disease as age distribution[3a] and geographic prevalence,[3b] in the gradation from frank to mild or suspected abortive forms of the disease, and in the development of serologic immunity in those who do not have the disease in recognizable form.[5] The limited and selective occurrence of the frank disease, however, is apparent in the tendency to familial occurrence,[4] in seasonal and climatic variations in the frequency with which exposure to the virus results in the paralytic disease,[3b] in its occurrence following operations on the upper respiratory mucous membrane[6,7,11,25] and in its association with pregnancy.[3c,e]

That poliomyelitis occurs excessively often during the latter months

of pregnancy is a clinical impression which is in conformity with the view that endocrine differences are involved in susceptibility to the virus. Among the changes which accompany pregnancy are those of mucous membrane, which are attributed to alterations in the economy of estrogenic substance.

The weight of evidence in poliomyelitis implicates the nasal mucosa as a portal of entry of the virus. That a disturbance of this structure may open up the pathway for the entrance of the infectious agent is strikingly shown in the occurrence of bulbar poliomyelitis following tonsillectomy and adenoidectomy. Thus, the suspected selectivity seen in the occurrence of paralytic poliomyelitis in the latter half of pregnancy suggests the involvement of estrogenic substance in susceptibility, and gives some indication as to the possible manner of its operation: through mucous membrane alterations.

While no weight can be given to single instances, there are two occurrences of poliomyelitis recorded in endocrinopathic individuals which, because of the uncommonness of the disease and the even greater rarity of the endocrinopathies in the general population, are impressive when taken together. In four types of "juvenile adiposogenital hypopituitarism" cited in a study,[12] one had suffered an attack of poliomyelitis. The other instance is an attack of poliomyelitis in an adult male castrate individual seen by the author.

Experimentally, it has been shown that castration of immature female monkeys (Macacus rhesus) results in thinning of the genital mucosa, and that the administration of estrogens to such animals effects a recornification of the genital mucosa.[1] The nasal mucosa participates in these changes.[22]

Experiments have been reported by the author[3c] in which castrate immature female monkeys developed poliomyelitis following intranasal instillation of virus more promptly and with greater frequency than castrate immature female monkeys prepared by preliminary injections of estrin (Amniotin Squibb), and the reaction maintained through the period of virus instillations. Exact comparison could not be made between these results and our general experience with intranasal instillation of virus because of difference in experimental set-up, but there was a pronounced dissimilarity between the results in castrate monkeys and estrin-treated castrate monkeys. Whether the castrate animals were more susceptible than normal animals, or the estrin-treated animals more resistant was not clear. However, our interpretation in view of general experience with intranasal instillations of virus, and perhaps influenced to an extent by theoretical reasons for believing that castration would enhance susceptibility and that administration of estrin would heighten resistance, was that each procedure affected susceptibility.

Later experiments[3d] showed that the injection of estrogenic substance into castrate female monkeys enhanced resistance to intranasal instillation of the virus, these animals not only developing experimental poliomyelitis with less frequency than the controls, but the interval from the first instillation of virus to the onset of the disease was comparatively longer.

It is not known whether, on the one hand, the experimental conditions are optimal, or whether, on the other hand, they are entirely

artificial and beyond the bounds of what could exist in individuals exhibiting the manifestations seen in the suspected poliomyelitis susceptible type. However, since the experimental observations are consistent with epidemiologic implications, it is believed that the artificially induced conditions may be considered as reflecting those which exist in individuals susceptible to poliomyelitis.

Comparative urinary estrogen assays were done on poliomyelitis patients and control individuals at the Massachusetts Hospital School for Crippled Children, Canton. Urinary specimens were collected in a uniform manner from poliomyelitis patients and others of the same ages, and estrogen assays made by benzol extraction[17] and titration by the vaginal smear method.[24]

These assays were made on chronic cases, so the status at the time of the test does not necessarily reflect the condition of the patient at the time of the attack of poliomyelitis, which in these individuals had been from 1 to 20 years previously. Neither is there anything to show that the endocrine condition indicated is not a sequela to poliomyelitis. However, in view of epidemiologic considerations, we are inclined to interpret the results as reflecting a physiologic condition which already existed at the time of the attack, although the figures cannot be considered conclusive because of the wide range of variability between individuals even of the same age. In view of the enhanced resistance to intranasal instillation of the virus observed in castrate monkeys treated with estrogen, the finding of a higher average excretion of estrogenic substance in the group of poliomyelitis patients suggests the possibility that the endocrinopathy sought as the basis of autarceologic susceptibility does not lie in a simple deficiency in the elaboration of estrogenic substance, but rather in some discrepancy in its economy.

Obviously, a great deal of research must be carried on before a satisfactory solution will be obtained to the problem of urinary assays for sex hormones. Gustavson and D'Amour[14] have recently reviewed the difficulties of the methods of assay. They point out that estrone (theelin) and estriol (theelol) are found in human urine almost entirely conjugated with glycuronic acid. The glycuronides must be hydrolyzed by acidifying the urine and heating before the estrogens can be extracted with immiscible solvents. Long boiling results in destruction of the estrogens. A compromise therefore has to be established between complete hydrolysis and minimum destruction.[13,15] Marrian[20] adjusted the pH to about 1 and then heated the material in an autoclave at 120° C. for 2 hours.

It is of the utmost importance to repeat various methods of assay for total estrogenic content in exactly the manner reported by the original author if the results are to be comparable. Furthermore, the separation of the different estrogens before assaying the extract would give much more fundamental data.

In assaying androgens, the period of boiling must be limited to 15 minutes if losses by destruction are to be avoided.[21] The problem of assaying the crude extract from urine is fraught with many difficulties.[2]

During the period in which the author has been engaged in the study of poliomyelitis, now extending over 25 years, he has had many

opportunities such as pointed out by Draper as "almost essential to be powerfully impressed by this quality of the human being" and has come to agree that patients with poliomyelitis tend to be of a different stripe than other individuals.[3d] Although supported only in part by actual measurements,[3c,10] the impression is that the characteristics of such a type are discernible in cases of poliomyelitis, most often in older boys and least often in younger girls.

But in this day of tests, measurements and assays, with insistence on statistical proof, clinical impressions lack convincingness. Measurements are too involved for general workability. Endocrinologic assays are not yet sufficiently seasoned for practical application. A test of the clinical impression itself, which at least has the advantage of being workable, is a simple numerical count of the frequency with which it is possible to select correctly the certain type of individual in which poliomyelitis occurs. We have attempted by this means to return to the basic question: Are those individuals attacked by poliomyelitis of a different stripe?

Observations have been made of 1,004 patients or photographs of patients with various crippling conditions, and those who appeared to be of the type prone to paralytic poliomyelitis have been separated from the others. The data represent 19 cases of poliomyelitis and 31 cases of other crippling conditions seen at the Shriner's Hospital, Springfield, Mass., in 1941; and 243 photographs of 177 cases of poliomyelitis, and 711 photographs of 520 cases of other crippling conditions admitted to the Massachusetts Hospital School for Crippled Children, Canton, Mass., from 1913 to 1941. Where more than one photograph of a case was available, readings were made at separate times, and with no knowledge of previous inspection. That the readings are not haphazard, but represent a selection of characteristics seen in the photographs is shown by the fact that, in a high percentage of the cases, second, third and sometimes even fourth photographs of the same individual were given the same reading, both where the selection was right and where it was wrong. In relatively few instances, subsequent readings on photographs were reversed.

Where the patients themselves were seen, all manifestations of the disease, for example a paralyzed arm or leg or an amputation, were entirely concealed. In the photographs, the whole was covered except the face. Inspection of photographs of face only is probably a severe test as to whether or not a selection can be made between the types of individuals having poliomyelitis and those with other crippling diseases: first, because some of the living form and expression is doubtless lost in a photograph, and, secondly, because body configuration is also in considerable part the basis of the clinical impression.* As a matter of fact, the comparatively higher proportion of correct selections among the patients who were seen indicates that there is something in the living ensemble which may not be evident in a photograph of the face.

The results of attempts to differentiate "poliomyelitis type" indi-

* After the readings herein recorded were completed, as a test a few erroneous readings given in the paper were made correctly when the body was exposed to view, and in a few instances where the type was particularly striking, patients recorded as admitted for other diseases were determined to have also had poliomyelitis.

viduals from patients with other crippling diseases are given in Table 1 by sex and age groups. It may be seen that inspection of patients themselves (Springfield group) resulted in a fairly sharp division. When photographs were used (Canton group) the selection was not as high, although the picking of the "poliomyelitis type" shows a positive correlation with the individuals who actually were patients with poliomyelitis in all of the age groups except girls under 10 years.

TABLE 1.—DIFFERENTIATION BY FACIAL CHARACTERISTICS BETWEEN INDIVIDUALS WITH POLIOMYELITIS AND OTHER CRIPPLING CONDITIONS.

| | | No. of tests. | Results of tests. | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total. | | Males. | | | | | | Females. | | | | | |
| | | | | | All. | | 10 yrs. and over. | | Under 10 yrs. | | All. | | 10 yrs. and over. | | Under 10 yrs. | |
| | | | + | − | + | − | + | − | + | − | + | − | + | − | + | − |
| Springfield | P | 19 | 14 | 5 | 5 | 3 | 4 | 3 | 2 | 0 | 8 | 2 | 5 | 0 | 3 | 2 |
| | NP | 31 | 8 | 23 | 4 | 6 | 2 | 5 | 2 | 1 | 4 | 17 | 3 | 7 | 1 | 10 |
| Canton | P | 243 | 90 | 153 | 46 | 84 | 32 | 48 | 14 | 36 | 44 | 69 | 33 | 42 | 11 | 27 |
| | NP | 711 | 169 | 542 | 79 | 319 | 43 | 194 | 36 | 125 | 90 | 223 | 46 | 148 | 44 | 75 |
| Total | P | 262 | 104 | 158 | 52 | 87 | 36 | 51 | 16 | 36 | 52 | 71 | 38 | 42 | 14 | 29 |
| | NP | 742 | 177 | 565 | 83 | 325 | 45 | 199 | 38 | 126 | 94 | 240 | 49 | 155 | 45 | 85 |
| Total | | 1004 | 281 | 723 | 135 | 412 | 81 | 250 | 54 | 162 | 146 | 311 | 87 | 197 | 59 | 114 |

P = Poliomyelitis. NP = Other crippling conditions.
\+ = Facial characteristics suspected as being associated with susceptibility to paralytic poliomyelitis.
− = Facial characteristics not associated with poliomyelitis.
Springfield = patients seen. Canton = photographs of patients seen.

The method of selection is open to the criticism, of course, that such a test is the actual reading of some result of poliomyelitis. It is often pointed out, for instance, "They are fat because they are in a wheelchair." The objection that the decisive characteristics in the poliomyelitis cases are not merely results of the attendant physical handicap is met, at least to some extent, by the fact that the control groups comprised equally physically handicapped individuals.

That characteristics which tend to be associated with poliomyelitis have been picked, rather than those accompanying or resulting from any of the other crippling diseases rejected, is shown by the fact that the percentage of selection of persons of the poliomyelitis type in the poliomyelitis group was 39.7%, while for the five other groups the figure fell to between 18.2 and 26.6% (Table 2). In other words, the differentiation was approximately equal in all of the groups of other crippling conditions.

It might well be suspected that in some instances actual effects of the disease formed the basis of differentiation, as for example particularly the group classified as "spastic." However, in all of the non-poliomyelitis groups the percentage of differentiation was lower. It should be stated that, whenever there was apparent evidence of disease

which could not be hidden, the cases were excluded by Dr. Nelson Hatt of the Shriner's Hospital, Springfield, and by Dr. John E. Fish, of the Massachusetts Hospital School for Crippled Children, Canton, and their staffs, and were not included in this study.

TABLE 2.—DIFFERENTIATION BY FACIAL CHARACTERISTICS BETWEEN INDIVIDUALS WITH POLIOMYELITIS AND OTHER CRIPPLING CONDITIONS BY DISEASE GROUPS.

| | No. of tests. | Results of tests. | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total. | | | Males. | | | | | | Females. | | | | | |
| | | | | | All. | | 10 yrs. and over. | | Under 10 yrs. | | All. | | 10 yrs. and over. | | Under 10 yrs. | |
| | | + | − | %+ | + | − | + | − | + | − | + | − | + | − | + | − |
| Poliomyelitis | 262 | 104 | 158 | 39.7 | 52 | 87 | 36 | 51 | 16 | 36 | 52 | 71 | 38 | 42 | 14 | 29 |
| Congenital deformities | 149 | 36 | 113 | 24.2 | 17 | 52 | 5 | 18 | 12 | 34 | 19 | 61 | 8 | 37 | 11 | 24 |
| Tuberculosis | 124 | 32 | 92 | 25.8 | 15 | 58 | 10 | 38 | 5 | 20 | 17 | 34 | 12 | 24 | 5 | 10 |
| Osteomyelitis | 83 | 15 | 68 | 18.1 | 8 | 57 | 6 | 49 | 2 | 8 | 7 | 11 | 7 | 10 | 0 | 1 |
| Spastic paralysis | 82 | 17 | 65 | 20.7 | 8 | 32 | 5 | 17 | 3 | 15 | 9 | 33 | 3 | 16 | 6 | 17 |
| Rickets | 68 | 15 | 53 | 22.1 | 3 | 27 | 0 | 6 | 3 | 21 | 12 | 26 | 2 | 15 | 10 | 11 |
| Obstetrical paralysis | 18 | 4 | 14 | 22.2 | 0 | 8 | 0 | 6 | 0 | 2 | 4 | 6 | 1 | 3 | 3 | 3 |
| Miscellaneous | 218 | 58 | 160 | 26.6 | 32 | 91 | 19 | 65 | 13 | 26 | 26 | 69 | 16 | 50 | 10 | 19 |

\+ = Facial characteristics suspected as being associated with susceptibility to paralytic poliomyelitis.
− = Facial characteristics not associated with poliomyelitis.

TABLE 3.—DIFFERENTIATION BY FACIAL CHARACTERISTICS BETWEEN INDIVIDUALS WITH POLIOMYELITIS AND OTHER CRIPPLING CONDITIONS. DEGREE OF CORRECTNESS ACCORDING TO AGE AND SEX.

| | No. of tests. | Results of tests. | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total. | | Males. | | | | | | Females. | | | | | | |
| | | | | All. | | 10 yrs. and over. | | Under 10 yrs. | | All. | | 10 yrs. and over. | | Under 10 yrs. | |
| | | R | W | R | W | R | W | R | W | R | W | R | W | R | W |
| Poliomyelitis | 262 | 104 | 158 | 52 | 87 | 36 | 51 | 16 | 36 | 52 | 71 | 38 | 42 | 14 | 29 |
| Non-poliomyelitis | 742 | 565 | 177 | 325 | 83 | 199 | 45 | 126 | 38 | 240 | 94 | 155 | 49 | 85 | 45 |
| Total | 1004 | 669 | 335 | 377 | 170 | 235 | 96 | 142 | 74 | 292 | 165 | 193 | 91 | 99 | 74 |
| Per cent R | | 66.6 | | 68.9 | | 71.0 | | 65.7 | | 63.9 | | 68.0 | | 57.2 | |
| Per cent + in total* | | 28.0 | | 24.7 | | 24.5 | | 25.0 | | 31.9 | | 30.6 | | 34.1 | |
| Per cent poliomyelitis in group | | 26.1 | | 25.4 | | 26.3 | | 24.1 | | 26.9 | | 28.2 | | 24.9 | |

R = Selection according to type agreed with actual diagnosis.
W = Selection according to type did not agree with actual diagnosis.
* = Percentage of individuals in poliomyelitis and non-poliomyelitis groups selected as having the characteristics associated with susceptibility to paralytic poliomyelitis.

In Table 3 are shown the various groups by sex and age, according to "right" or "wrong" selection. It may be seen that the percentage of cases of poliomyelitis was approximately the same in all of the groups. The degree of correctness of selection was highest in boys 10 years of age and over; then, in order, in boys under 10 years, in girls 10 years and over, and lowest in girls under 10 years. Thus, the chances of a correct selection vary with the different age groups because of the assignment of different proportions of cases to the type in question. As may be seen from the table, the actual outcome shows that for boys 10 years and over, the correctness of the selection may be represented as 71%; for boys under 10 years, 65.7%; for girls 10 years and over, 68%; as compared with 57.2% for girls under 10 years. Thus, in all groups except younger girls, where the figures correspond with chance distribution, a partial distinction was made between poliomyelitis and other crippling conditions by this method; and in males and females over 10 years of age, it was "statistically significant."

**Conclusions.** Observations have been made on 1,004 patients or photographs of patients with various crippling conditions, to test the clinical impression that paralytic poliomyelitis exhibits a tendency to selective occurrence in certain types of individuals. The significant proportion of correct readings obtained confirms this impression and verifies Draper's concept of a "poliomyelitis type,"[9a] as well as anthropometric studies indicating a difference in bodily measurements from the normal.[3c,10] They are additional evidence in support of the epidemiologic observation that the frank disease tends to occur in but a limited and selected fraction of those exposed; they are consistent with the evidence presented elsewhere that these individuals are possessed of an autarceologic susceptibility,[3b,c] as shown by the tendency of the disease to familial aggregation,[4] and that the character in question is a physiologic difference of an endocrine nature[3c] which, although to a considerable extent subclinical, manifests itself in the clinically discernible characteristics of the individuals: to a slighter degree in younger girls, moderately in younger boys and older girls, and to a still greater degree in boys 10 years of age and over.

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Correction.—In their review "The Trivalent Arsenicals in Syphilis" (Am. J. Med. Sci., **201**, 611, 1941) Stokes and Beerman (p. 622), erroneously state that Young and McClendon quote Goldman "as rating Mapharsen as immeasurably more effective than quinine in quartan infections, and notably more effective than arsphenamine and neoarsphenamine." It should read " . . . . *tertian* infections."

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